ANNUAL REPORT
National Eye Institute
October 1, 1985 - September 30, 1986

REPORT OF THE SCIENTIFIC DIRECTOR
Jin H. Kinoshita, Ph.D.

During this past year considerable restructuring of the intramural program has taken place. The Laboratory of Vision Research (LVR) has been divided into smaller working units. During the course of years the LVR accumulated a number of unrelated research groups making the Laboratory difficult to manage. Creating smaller units of scientists with similar interests strengthens the interaction and helps the head of the Laboratory to be more responsive to the needs of his group. Three additional laboratories, Laboratory of Retinal Cell and Molecular Biology, Laboratory of Immunology and Laboratory of Mechanisms of Ocular Diseases have been created. These laboratories join the Clinical Branch, Laboratory of Sensorimotor Research, Laboratory of Molecular and Developmental Biology and Laboratory of Pathology to constitute the seven branches of the NEI Intramural Program. We feel the reorganization makes for a more efficient means of managing the research activities on the Bethesda campus.

During the year significant progress has been achieved in many research areas. To illustrate this point four studies will be cited in this report even though there are several other intramural studies which are equally impressive.

For a number of years Dr. Robert Nussenblatt, Dr. Igal Gery and their associates have been developing experimental animals models which simulate the inflammatory eye diseases known as uveitis. The most promising approach was found to be the injection of a purified retinal protein, identified as S antigen, into Lewis rats, guinea pigs and monkeys. Animals immunized with S antigen developed clinical anterior and posterior uveitis which was confirmed by histology. The monkey model closely resembled the disease found in posterior uveitis patients. Additional experimental study suggested to the group that T-cells were involved in this ocular inflammatory process. Since cyclosporine, a complex peptide isolated from a certain fungus, was known to suppress T-cell activity, the NEI scientists thought of the possibility that cyclosporine may alleviate this inflammatory eye process. Remarkably the cyclosporine treatment completely prevented the S-antigen induced uveitis in animals.

The laboratory studies encouraged Dr. Nussenblatt to test the effectiveness of cyclosporine in patients with various types of uveitis. Preliminary studies suggested that patients

with the inflammatory disorder known as Behcet's disease were particularly responsive to cyclosporine treatment in that the inflammatory process was dramatically alleviated. These findings served as the basis for a full-scale randomized clinical trial of cyclosporine as a method of treatment of Behcet's patients. Dr. Nussenblatt arranged to have this trial conducted as a multi-center study in Japan where there is greater prevalence of these Behcet's cases than in this country. This study was concluded recently and positive results were obtained indicating that cyclosporine is indeed effective against this form of uveitis. Thus, the series of studies which began in the laboratory has led to the development of a treatment of an inflammatory eye disease where no specific treatment was known before.

For his contributions for the development of cyclosporine as a therapeutic agent of uveitis Dr. Robert Nussenblatt will be honored by the Japanese Ophthalmological Society in 1987.

Dr. Piatigorsky and associates of the LMDB have been developing transgenic mice which have been used in an exciting study that potentially has clinical relevance. These mice permit the analysis of DNA sequences which are responsible for the expression, tissue-specificity and developmental program of gene expression. In their investigations they identified numerous putative regulatory regions of the genes for a specific lens protein, the α A-crystallin. Furthermore, transient expression experiments using explanted lens epithelia have provided evidence that these DNA sequences are indeed responsible for the tissue-specific expression of the crystallin genes. Recently, they created a DNA containing the α A-crystallin gene promoter (only 364 nucleotides) fused with the bacterial chloramphenicol acetyltransferase gene (CAT). They injected this recombinant DNA into the nucleus of a fertilized mouse egg and produced a male transgenic mouse which had CAT activity in its ocular lens and only in the lens. None of the 9 other tissues examined contained CAT activity. This clearly permits further analysis of the molecular nature of tissue-specific crystallin gene expression at the level of the whole organism. Moreover, it kindles hope for eventual gene therapy of ocular diseases.

For his many important contributions of the application of molecular biology to the eye, Dr. Piatigorsky was the recipient of the 1986 Friedenwald Award, one of the prestigious awards presented by the Association for Research in Vision and Ophthalmology.

Major advances in the study of gyrate atrophy have been made by a team of scientists led by Dr. Muriel Kaiser-Kupfer. Gyrate atrophy is a rare hereditary disease which leads to the degeneration of the retina and choroid. This team of scientists has shown that this disorder is caused by a deficiency of the enzyme ornithine aminotransferase (OAT)

which results in a hyperornithinia in these patients. Dr. Kaiser-Kupfer has shown that diets which restrict the sources of ornithine seem to protect and even improve visual function.

Stimulated by these clinical studies, Dr. George Inana and his colleagues began examining the gyrate atrophy problem using DNA technology. They have been successful in isolating a cDNA clone for human OAT. With this probe they are studying the nature of the OAT gene defect in gyrate atrophy patients. This study is an example of how rapidly a clinical problem can be attacked with the most modern of research tools because of the unique setting of the intramural program which fosters the interactions of scientists from many disciplines.

For the development of the first cDNA probe to study an ocular disease Dr. George Inana was honored as the principal guest lecturer at the Proceedings of the Japanese Chapter of the International Society of Eye Research in Sendai, Japan in 1985.

Dr. Wurtz has pioneered studies on the understanding of how the brain uses visual information to produce eye movements. His recent work, using old world monkeys as a model system, has had two facets. First, he has extended his analyses of the brain circuits that produce the rapid or saccadic eye movements that move the eye quickly from one part of the visual field to another. His studies were the first to recognize that the basal ganglia of the brain participated in controlling saccadic eye movements. The basal ganglia produce a tonic inhibition on the saccadic control system of the brainstem, the superior colliculus. In addition his recent findings revealed that the neuronal transmitter is likely to be GABA since he has been able to inhibit or facilitate eye movements by injecting minute quantities of GABA agonists or antagonists into the terminal area of basal ganglia fibers in the superior colliculus. Thus, a major new control system acting on the initiation of saccadic eye movements has been revealed. His second series of experiments has been on a second type of eye movement, the pursuit eye movements that allow the eye to track moving targets. Dr. Wurtz's group has shown that these movements are normally dependent for their visual input on a tiny area of cerebral cortex that is devoted to processing of visual motion information. Furthermore, minute damage produced by microliter injections of a neurotoxic chemical into adjacent regions produces the directional deficit in pursuit eye movements seen in human patients with cerebral damage. These experiments show for the first time the precise localization and function of the cerebral cortical areas upon which pursuit eye movements are dependent.

For these accomplishments Dr. Wurtz was honored by the European Neuroscience Association which has designated him to present the Gordon Holmes Lecture at the meeting of the Association in September, 1985.

Although the intramural program faces difficult times ahead because of restrictions in budget, personnel and space it is encouraging that accomplishments like those cited here can be achieved. This is a tribute to the intramural scientists with their talents and enthusiasm who devote their lives to dispel our ignorance in many problems related to the eye.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00065-09 OSD

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Physiological Studies of the Primate Visual System

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)

PI:	Francisco de Monasterio	M.D., Sc.D	Medical Officer	OSD, NEI
Others:	Edna P. McCrane	B.S.	Biologist	OSD, NEI

COOPERATING UNITS (if any)

Howe Laboratory, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

LAB/BRANCH: Office of the Scientific Director

SECTION:

INSTITUTE AND LOCATION: NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.90	0.40	0.50

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project involves the study of the physiological organization of neurons of the visual system of primates. We have examined the functional mapping on the striate cortex of the innervation density mediated by the two major classes of ganglion cells that respectively project to the parvocellular and magnocellular layers of the lateral geniculate nucleus. We have found that the mannification in striate cortex is proportional to the afferent density of one cell type, and that the so-called point-image area of striate cortex follows the reciprocal of the afferent density of the other cell type. These differences between neural maps are likely to have psychophysical consequences. In addition, an electrophysiological survey of the variation of receptive-field size with eccentricity is in progress, and we have begun preliminary recordings in striate and extrastriate cortex to examine chromatic cell properties. Finally, we are completing analyses of previous studies for their publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00135-14 OSD

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biochemistry of Retina and Pigmented Epithelium in Health and Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Helen H. Hess M.D. Medical Officer (Research) OSD, NEI

COOPERATING UNITS *(if any)*
Veterinary Resources Branch, DRS, NIH

LAB/BRANCH
Office of the Scientific Director, NEI

SECTION

INSTITUTE AND LOCATION
National Eye Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.4	1.0	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of nutrition, oxidation, and other environmental factors (light intensity or darkness) on the incidence and progress of posterior subcapsular opacities (PSO) associated with retinal degeneration are being studied in Royal College of Surgeons (RCS) rats, in which rod photoreceptor outer segment debris accumulates secondary to a phagocytic defect in the retinal pigmented epithelium. Evidence has been obtained that oxidative changes in polyunsaturated fatty acids in the debris lead to water-soluble toxic aldehydes that can be detected in the vitreous, and are toxic to lens membranes. Several diets have been found to prevent mature cataracts, and dark-rearing has been shown to prevent the PSO detectable microscopically. By exposing pink-eyed dystrophic rats to constant light of 25 footcandles beginning (1) at 20-23 postnatal days or (2) at birth, we have been able for the first time to demonstrate histopathological changes similar to those in some naturally occurring human posterior subcapsular cataracts (PSC), such as those seen in retinitis pigmentosa. Lens epithelial cells migrated to the posterior pole of the lens. Many were bizarre in shape, with abundant pale-staining cytoplasm and small (or large) nuclei ("bladder cells of Wedl"). Changes similar to human anterior subcapsular cataracts were also noted. RCS rats provide a readily manipulated animal model of PSC, exacerbated by some environmental factors and prevented by others. Principles established with the model may have significance for slowing or preventing human PSC.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1984 - September 30, 1986

REPORT OF THE DEPUTY CLINICAL DIRECTOR
Robert B. Nussenblatt, M.D.

The Clinical Branch consists of three Sections, each with its own Section Head: Section on Ophthalmic Genetics and Pediatric Ophthalmology, Muriel I. Kaiser-Kupfer, M.D.; Section on Neuro-ophthalmology, James Carl, M.D.; and the Section on Retinal and Vitreal Diseases, Robert B. Nussenblatt, M.D. (Acting).

The Section on Ophthalmic Genetics and Pediatric Ophthalmology continues its long-term interest in gyrate atrophy. Patients placed on a low arginine, low protein diet with supplemental amino acids continue to be observed. The group has also been actively pursuing better ways to control the deposition of cystine crystal in the cornea of patients with cyctinosis. Patients with this recessively inherited storage disease will accumulate nonprotein cystine within cellular lyposomes. The ocular manifestations of this disorder include photophobia, crystal deposition in the cornea, conjunctiva, iris, and depigmentation of the retina. A masked randomized clinical trial using topical cysteamine has begun, in order to answer the question of whether this approach will prevent further deposition of crystals in the corneas of cystinosis patients. Another important area of research includes the documentation and monitoring of opacities in the human lens, of great import with the potential availability of medications that may be of use in treating cataract formation.

The Section on Retinal Diseases and Vitreous remains heavily involved with two long term clinical trials. Sorbinil, an aldose reductase inhibitor given orally, is being tested in a randomized masked study to see if it will inhibit the development of diabetic retinopathy. Additionally, patients with senile macular degeneration continued to be studied in this randomized masked study in order to test the efficacy of vitamin E and C therapy as well as the prevention of damage from light below 500 nanometers in preventing this degenerative process, the leading cause of newly registered blindness in the white adult population in the United States. The results of these two most important trials will not be available for some time to come. In addition, this group has studied the amount of flourescein leakage into the vitreous of diabetic patients, using the vitreous fluorophotometer. Diabetic patients with no microaneurysms have not demonstrated greater posterior vitreous leakage as compared to controls. However, differences in vitreal leakage can be noted in diabetic patients with minimal background retinopathy when compared to controls.

The Neuro-ophthalmic Section has concentrated its efforts in two major areas. They have devoted their efforts at developing methods for the analysis of oculomotor disorders in human subjects. This has led to a computerized facility which can stimulate an eye muscle weakness in normals using optical means studies on congenital nystagmous which have shown that these patients

with an abnormality of their vestibulo-ocular reflex, and that some may use this poor response to help them improve acuity by head shaking. Clonazepam has been seen to quiet a variety of types of nystagmus.

The Clinical Branch reflects new horizons with basic research observations playing an increasingly greater role in the research being conducted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00213-01 CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Sensory and oculomotor contributions to ocular disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Kent E. Higgins	Ph.D.	Expert	CB, NEI
Others:	Rafael C. Caruso	M.D.	Visiting Scientist	CB, NEI
	Edmond Thall	M.D.	Staff Fellow	CB, NEI
	Monique S. Roy	M.D.	Visiting Scientist	CB, NEI
	Francisco de Monasterio	M.D.	Medical Officer	OSD
	Robert Nussenblatt	M.D.	Deputy Director	CB, NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Clinical Branch

SECTION
Office of the Clinical Director

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.97	1.07	0.90

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
- [X] (a1) Minors
- [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Spatial contrast sensitivity was used to assess losses or changes in overall visual resolution in patients having a variety of toxic, inflammatory, degenerative, or congenital retinal and neuro-ophthalmological disorders of the visual system. A criterion-free forced-choice psychophysical procedure was used, since this method was previously shown to minimize false positive or false negative diagnoses at initial test and to minimize spurious changes in sensitivity with repeated testing. Contrast sensitivity testing, while requiring more patient testing time, continued to be superior to conventional acuity measuremetns for the detection of early losses and for monitoring changes in visual resolution in patients undergoing treatment. Age-referenced normative data make it possible to distinguish contrast sensitivity loss due to ocular disorder from that expected on the basis of normal aging.

A retinal image stabilization system was used in conjunction with the spatial contrast sensitivity test system to carry our preliminary research on normal subjects using artificial scotomata and complex spatial luminance profiles to examine interactions among fixational errors, eye movements, and visual field defects. This system is currently being modified to permit focal electro-retinography and high resolution microperimetry in small, localized regions of the retinas in Eye Clinic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00214-01 CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Acquired and congenital color vision deficiencies: Mechanisms and diagnosis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Kent E. Higgins	Ph.D.	Expert	CB, NEI
Others:	Kenneth B. Knoblauch	Ph.D.	Staff Fellow	CB, NEI
	Edmond Thall	M.D.	Staff Fellow	CB, NEI
	Francisco de Monasterio	M.D.	Medical Officer	CB, NEI
	Rafael C. Caruso	M.D.	Visiting Scientist	CB, NEI
	Robert Nussenblatt	M.D.	Deputy Director	CB, NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Clinical Branch

SECTION
Office of the Clinical Director

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.2	1.1	0.1

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project involves the study of cone function in cases of color vision defects, with special emphasis on the acquired color deficiencies. Human subjects have been used for these studies which range from attempts to improve quantification of data from existing standardized tests of color vision to the collection of additional data for the purpose of designing better tests for detecting color defects secondary to ocular disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00117-06 CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Oculomotor Disorders in Human Subject

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	James R. Carl	M.D.	Acting Head, Section on Neuro-ophthalmology	CB, NEI
Others:	Jon N. Currie	F.R.A.C.P.	Visiting Scientist	CB, NEI
	Victor Matsuo	Ph.D.	Senior Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*

Laboratory of Sensorimotor Research (R. Gellman, E. FitzGibbon, M. Goldberg); Department of Neurology, Johns Hopkins Hospital (D. Zee).

LAB/BRANCH
Clinical Branch

SECTION
Section on Neuro-Ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The major emphasis of this project has been on developing methods for analyzing oculomotor disorders in human subjects. Further development of the computerized system for stimulus presentation and eye movement recording has enabled us to present brief sets of visual tasks and collect data to evaluate each of the ocular motor subsystems. Additional work on the analysis programs has increased the sensitivity of these tests.

A second phase of the project has been to develop a detailed data base of normal human responses to various stimuli. We have recently concentrated on smooth pursuit eye movements, which have not previously been well characterized.

The computerized facility has allowed us to simulate an eye muscle weakness in normal subjects by optical means, and we found that subjects were able to alter the long latency pursuit response, but not the short latency one, to correct for the simulated weakness. These tests have been applied to a few patients with pursuit disorders and both short and long latency responses were abnormal.

Studies on congenital nystagmus were completed after finding that these patients often have an abnormality of the vestibulo-ocular reflex, and that some may use this poor vestibular response to help them improve acuity by head shaking. Other observations included: benefit of clonazepam in quieting a variety of types of nystagmus, continued analysis of horizontal saccadic abnormalities in all types of Gaucher's disease, and development of abducting nystagmus in multiple sclerosis patients as a result of adaptive changes after eye patching.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00160-04 CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Visual Inattention After Posterior Cerebral Hemisphere Lesions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	James R. Carl	M.D.	Acting Head, Section on Neuro-ophthalmology	CB, NEI
Others:	Jon N. Currie	F.R.A.C.P.	Visiting Scientist	CB, NEI
	Victor Matsuo	Ph.D.	Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*
Laboratory of Sensory Motor Research, NEI (D.L. Robinson, S.E. Peterson, M.E. Goldberg, E.J. FitzGibbon)

LAB/BRANCH
Clinical Branch

SECTION
Section on Neuro-ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.5	.5	

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Attentional mechanisms important in visual behavior were studied in patients with a variety of central nervous system abnormalities.

Shifts of visual attention as measured by reaction times were measured in patients with parietal lobe damage, and compared to patients with frontal lobe damage, Alzheimer's disease, or schizophrenia.

The patients with parietal lobe dysfunction demonstrated particular difficulty in shifting attention away from the ipsilateral visual field, and this finding was a reliable indicator of parietal cortical dysfunction.

Male patients with idiopathic hypogonadotrophic hypogonadism also had abnormal responses: they were slow in responding to targets in their right visual field.

Eye movements were evaluated in these patient groups, with pursuit movements and fixational stability emphasized. In some patients, square wave jerks present during fixation and reading were indications of attentional disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00162-04 CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Vitreous Fluorophotometry

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Monique Roy M. D. Visiting Scientist CB, NEI

COOPERATING UNITS (if any)

None

LAB/BRANCH

Clinical Branch

SECTION

Section on Retinal and Vitreal Diseases

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.50	1.50	0.00

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Vitreous fluorophotometry has been performed in patients with diabetes mellitus without retinopathy, patients with diabetes mellitus with nonproliferative retinopathy, and normal volunteer subjects, age- and sex-matched to the patients. The amount of fluorescein leakage into the vitreous of patients has been compared to that of the normal subjects. Correlations with other features of diabetes, such as the quality of diabetic control, the existence of subclinical neuropathy and nephropathy, and others were sought.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 000198-03 CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Sorbinil Retinopathy Trial

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Monique Roy	M. D.	Visiting Scientist	CB, NEI
Others:	Manuel Datiles	M. D.	Staff Ophthalmologist	CB, NEI
	James Carl	M. D.	Senior Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*
Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH (R. Silverman)

LAB/BRANCH
Clinical Branch

SECTION
Section on Retinal and Vitreal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.35	1.25	1.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Oral sorbinil, an aldose reductase inhibitor, will be administered in a double-masked randomized trial to diabetics with no or minimal diabetic retinopathy. This will be done to evaluate the effects of sorbinil on the development of diabetic retinopathy and further investigate the safety and toleration of sorbinil. The study will be conducted simultaneously in 11 research centers in the USA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00187-03-CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Effects of Corneal Contact Lenses on the Cornea

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN YEARS	PROFESSIONAL	OTHER
.2	.10	.1

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Short- as well as long-term effects of contact lens wear on the cornea are being investigated. Changes in corneal curvature, changes in corneal epithelial morphology and changes in corneal endothelial cell morphology are being studied by specular microscopy.

These data will help us understand the dynamics involved in the interaction between a contact lens and the cornea, the risk involved to corneal tissues, and how a systemic or local disorder may increase these risks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00188-03 CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Documentation and Monitoring of Opacities in the Human Lens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Robert Sperduto	M.D.	Head, Epidemiology Branch	BEP, NEI
	Peter Kador	Ph.D.	Head, Section on Molecular Pharmacology	LMOD, NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI

COOPERATING UNITS *(if any)*
Image Processing and Analysis Laboratory, DCRT, NIH (Benes Trus, Ph.D., Chief)

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN YEARS	PROFESSIONAL	OTHER
.7	.5	.2

CHECK APPROPRIATE BOX(ES)
- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are developing objective and subjective methods to monitor and document opacities in the human lens using different systems. We are presently actively recruiting patients with and without cataracts for reproducibility studies on the objective systems--the Scheimpflug cameras (Zeiss and topcon), Retroillumination camera (Neitz), Specular microscope (Keeler) and laser light-scattering spectroscope (KOWA). We will also test other systems using sound (ultrasonography), and nuclear magnetic resonance (magnetic resonance imaging). We are also studying subjective systems or method, such as the effects of cataracts on visual perception, contrast sensitivity, and glare, which may be useful as additional parameters in the monitoring of cataract presence, progression, or regression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00212-01 CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Model Program for Collaboration Between Cataract Surgeons and Ophthalmic Researchers

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Samuel Zigler	Ph.D.	Head, Section on Cataracts	LMOD, NEI
	Peter Kador	Ph.D.	Head, Section on Molecular Pharmacology	LMOD, NEI

COOPERATING UNITS (if any)

Consultants:	Jin H. Kinoshita	Ph.D.	Scientific Director	NEI
	George Inana	M.D., Ph.D	Head, Section on Molecular Pathology	LMOD, NEI

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.35	.35	

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
- [ ] (b) Human tissues
- [ ] (c) Neither
- [ ] (a1) Minors
- [ ] (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

There is presently an extreme dearth of human cataract material because of an abrupt shift of cataract surgical technique from intracapsular (intact lens) to extracapsular (fragmented lens), primarily because of advent of the use of intraocular lens. We are exploring ways by which fragmented lens materials can be maximally used in cataract basic research through close collaboration between cataract surgeons and basic researchers and modification of techniques by both groups.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00011-12 CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pigment Dispersion With and Without Glaucoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Sandeep Jain	M.D.	Visiting Fellow	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:
1.55	1.35	.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to compare patients with and without glaucoma having pigment dispersion syndrome. The data acquired may enable a determination of the risk of patients with pigment dispersion syndrome to developing glaucoma as well as add to understanding of the pathology of the the disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00062-10 CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Irido-Corneal-Endothelial (ICE) Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Carl Kupfer	M.D	Director	NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Manuel Datiles	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:
.35	.25	.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was formerly titled "Progressive Essential Iris Atrophy." Patients are being recruited with progressive essential iris atrophy with or without associated corneal disease. Information is being gathered to evaluate the clinical features and course of the disease process and to investigate aqueous humor dynamics in both affected and unaffected eyes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00083-09 CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Gyrate Atrophy of the Choroid and Retina

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Rafael Caruso	M.D.	Visiting Scientist	CB, NEI
	Kent Higgins	Ph.D.	Expert	CB, NEI

COOPERATING UNITS *(if any)*

The Howard Hughes Medical Institute Laboratory and the Department of Pediatrics, Johns Hopkins University, School of Medicine, Baltimore, Maryland (David L. Valle, M.D.)

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:
1.2	.7	.5

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [X] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with gyrate atrophy of the choroid and retina are examined systematically to confirm the diagnosis. Skin fibroblats of affected patients and family members are grown in tissue culture and assayed for ornithine aminotransferase activity. The results will be evaluated for correlation with the presence of homo- or heterozygosity for the disease trait. Patients will be given a trial of pyridoxine to see if serum concentration of ornithine can be reduced, and, if so, the patient will be classified as a "responder," and treatment with pyridoxine will be continued. Nonresponder and responder patients will be placed on a low arginine, low protein, diet with supplemental amino acids and observed for an arrest or improvement of their disease. If patients are not considered eligible for the diet or if they appear unable to comply with the dietary regimen they will be followed to record the natural progress of the condition. Patients with other forms of retinal degeneration, such as retinitis pigmentosa, fundus flavimaculatus, juvenile retinoschisis, are also examined and their courses are compared with gyrate atrophy patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00163-04 CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
NIH Interinstitute Medical Genetics Program: The Genetics Clinic

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Lessie McCain	R.N.	Clinical Technician	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN YEARS	PROFESSIONAL	OTHER
.15	.05	.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Interinstitute Medical Genetics Program and the Genetics Clinic, supported by the Clinical Center, offer a multidisciplinary approach to patients with genetic disease (Z01 CP 05139-04 CEB). Involved in the program are researchers from all Institutes. Patients evaluated in the clinic reporsent a broad spectrum of genetic disease. During the last year, approximately 423 individuals were seen, representing approximately 100 different disease categories. Due to the high frequency of ocular involvement in many of the cases, almost all the patient were evaluated by Clinical Branch staff of were discussed in consultation. The Clinic serves as a source of interesting case material concerning patients with inherited or developmental abnormalities of the visual system.

In addition to the Genetics Clinic, patients are seen for genetic consultation at the Maryland School for the Blind. This experience has resulted the recruitment of patients into Clinical Branch protocols.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00172- 04 CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Senile Macular Degeneration

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Muriel I. Kaiser-Kupfer	M. D.	Head, Section on Ophthalmic Genetics	CB, NEI
Others:	Carl Kupfer	M. D.	Director	NEI
	Monique Roy	M. D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.43	0.43	0.00

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study will determine if patients with severe visual loss because of senile macular degeneration in one eye and with good vision in the second eye can be protected from severe visual loss in the good eye by the administration of vitamin E and vitamin C when exposure of the retina to light below 500 nanometers is diminished. The recruited patients will be randomly assigned either to a treated or an untreated control group and examined at four-month intervals. Follow-up will continue for five years, unless an early beneficial or detrimental effect causes the study to be terminated in less than five years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00123-06-CB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Psychophysics of the Visual System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Rafael C. Caruso	M.D.	Visiting Scientist	CB, NEI
	Kent E. Higgins	Ph.D.	Expert	CB, NEI
	Ralph D. Gunkel	O.D.	Ophthalmic Physicist	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN YEARS	PROFESSIONAL	OTHER
.65	.35	.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The visual function of patient with ocular diseases or lesions in the visual pathways and of normal subjects is measured with psychophysical techniques. These data are correlated with those obtained with electrophysiological tests of visual function. The results stained contribute to the diagnosis of ocular and neural disorders that affect vision, and are needed to characterize their nature and evolution. They are also valuable in the assessment of the effect of different forms of treatment on the outcome of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00144-05-CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders.)

Clinical Electrophysiology of the Visual System

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Rafael Caruso	M.D.	Visiting Scientist	CB, NEI
	Kent E. Higgins	Ph.D.	Expert	CB, NEI
	Doris J. Collie	A.A.	Health Technician	CB, NEI

COOPERATING UNITS (if any)

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.65	.35	.3

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The visual function of patients with ocular diseases or lesions in the visual pathways and of normal subjects is measured objectively with electrophysiological techniques. These data are correlated with those obtained with psychophysical tests of visual function. The results obtained contribute to the diagnosis of ocular and neural disorders that affect vision, and are needed to characterize their nature and evolution. They are also valuable in the assessment of the effects of different forms of treatment on the outcome of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00211-01 CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

A Double-Masked Controlled Randomized Clinical Trial of Topical Cysteamine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Manuel Datiles	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

Human Genetics Branch, NICHD, National Institutes of Health, Bethesda, Maryland (William Gahl, M.D., Ph.D.)

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER
.25	.15	.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Nephropathic cystinosis is an autosomal, recessively inherited storage disease in which nonprotein cystine accumulates within cellular lysosomes due to a defect in lysosomal cystine transport. Ocular manifestations include photophobia crystal deposits in cornea, conjunctiva iris and depigmentation of the retina. Systemic complications include the Fanconi syndrome, and renal failure.

Eight years ago cysteamine, a free thiol which depletes cystine from cells, was introduced in the therapy of cystinotic patients. Although patients had improved growth and stabilized renal function, there was no noticeable effect on the accumulation of corneal crystals. Recent studies showed that corneal cells in tissue culture are readily depleted of cystine by the introduction of cysteamine, making feasible the use of topical ophthalmic cysteamine to circumvent the humoral route. After appropriate animal studies to test for complications which revealed none, we have begun a double-masked clinical trial to test the efficacy of topical cysteamine in humans. Five patients have thus far been enrolled, outcome of the study awaits further observation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00084-08 CB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Anterior Chamber Anomalies Associated with Glaucoma or Ocular Hypertension

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Carl Kupfer	M.D.	Director	NEI
Others:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI
	Paul Edwards	M.D.	Visiting Fellow	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.65	0.55	.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

With recent embryological research indicating the role of the neural crest in contributing to all connective tissues anterior to the lens epithelium, the group of developmental anomalies of the anterior chamber with glaucoma or ocular hypertension is being reviewed.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1984 - September 30, 1986

REPORT OF THE CHIEF, LABORATORY OF IMMUNOLOGY

Robert B. Nussenblatt, M.D.

This past year was the first full year for the Laboratory of Immunology of the National Eye Institute. The year saw the establishment of four Sections within the Laboratory, each with its own Section Head: Section on Clinical Immunology, Alan G. Palestine, M.D., Section on Immunology and Virology, John J. Hooks, Ph.D., Section on Experimental Immunology, Igal Gery, Ph.D., and Section on Immunoregulation, Robert B. Nussenblatt, M.D.

The Section on Clinical Immunology has been particularly interested in new animal models for human intra-ocular inflammatory disease, as well as the role of the neuro-endocrine axis on the immune response. The Section has added insight into the underlying mechanisms of the intra-ocular inflammatory disease produced by endotoxin immunization. Class II antigen expression by nonimmune cells within the eye was noted in the iris and the ciliary body, though no T-cells were present in the inflammatory infiltrate; gamma-interferon, a T-cell product, is thought the most potent inducer of class II expression. Though corticosteroid therapy abrogated both the cellular infiltrate and class II expression, only the cellular infiltrate could be prevented when indomethacin was utilized. The role of class II antigen expression on nonimmune cells may play an important role in the localization of the immune response. In separate studies examining the role of pituitary hormones and their effect on the ocular immune response, the Section has noted that modulation of this system appears to have profound effects on the immune response. The concurrent use of bromocriptine, which blocks prolactin production by the pituitary, with a dosage of cyclosporine that ordinarily is not especially effective in preventing the S-antigen induced experimental uveitis model, proved extremely effective, with complete protection affected. These findings will have immediate clinical application, since manipulation of the neuroendocrine system will hopefully permit the use of lower dosages of cyclosporine, and thereby prevent cyclosporine induced nephrotoxicity. These findings suggest that we are just beginning to learn about the possible immunomodulative techniques which should lead to better therapeutic strategies.

The Section on Experimental Immunology has been actively involved in the evaluation of the immune response and how it relates to ocular antigens. The Section has had the opportunity to compare two models of human uveitis induced by two distinct retinally derived antigens, the retinal S-antigen and IRBP. It has been noted that the susceptibility to these diseases is different in lower mammals. Further, delineation of the new IRBP induced model revealed that it was T-cell mediated and that the disease could be actively transferred by lymphocytes. Further the disorder could be induced in monkeys. The disease was a granulomatous uveitis, bearing characteristics similar to such severe human conditions as sympathetic ophthalmia and Vogt-Koyanagi-Harada's disease.

The Section on Immunology and Virology has had a long term interest in the production of T-cell immunomodulators, particularly interferon, and the role these play in ocular structures. The group has recently demonstrated for the first time the presence of IFN-gamma and IL-2 at the site of a localized ocular autoimmune disease. Additionally, the evaluation of exocrine glands involved in Sjogren's syndrome is infiltrated predominantly with T-cells, the majority of which express class II antigens. Moreover, the glandular epithelial cells (ducts and acini) were induced to express these antigens as well. In order to better evaluate the retinal pigment epithelial cell, a cell with immune-like characteristics, the Section has produced the first monoclonal antibody which is directed solely at the human RPE, with studies using this new immune probe just beginning.

The Section on Immunoregulation has been evaluating, in an in vitro system, the role of ocular cells in enhancing an immune response. The development of T-cell lines specific to the retinal S-Ag, which are capable of inducing uveitis when transferred to a naive host, has permitted the Section to ask several questions concerning the interaction between immune cells and the eye. A stable long-term rat Muller cell line has permitted the Section to evaluate the interactions between these two pure cell populations. A profound inhibitory effect by these cells on the T-cell has been seen, suggesting that this may be a normal protection mechanism. However, alterations of the Muller cells' membrane can obviate this inhibitory effect. Understanding basic mechanisms in parasitic conditions has also been a major concern of the Section, particularly toxoplasmosis and onchocerciasis. Indeed, in the first immunohistologic study of ocular onchocerciasis, the group has seen that T-cells are the predominant immune cell present and that vascular endothelia, pericytes and fibroblasts in the eye express class II antigens. Studies in the use of cyclosporine for human intra-ocular inflammatory disease has yielded important information concerning the nephrotoxic effects of the drug. Renal biopsies of patients on cyclosporine have demonstrated alterations in renal morphology, supporting the concept that there is a reversible as well as an irreversible component to this secondary effect of the drug. Newer therapeutic strategies, such as the use of bromocriptine combined with cyclosporine as well as new attempts at evaluating the local efficacy of this drug are underway.

The Laboratory of Immunology's first year has produced significant observations both from a clinical and basic research point of view. A better understanding of the basic mechanisms of ocular inflammatory disease is imperative, and the groundwork has now been laid. Further, as with our initial observations with cyclosporine, we sincerely feel that the Laboratory's work will result in better directed and more effective therapies for a group of diseases that are most challenging.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00229-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Assessment of the Size of the Leak Induced in Retinal Vessels Using PITC-Dextrans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Susan Lightman	M.D.	Visiting Fellow	LI, NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Einar Stefansson	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.5	0.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Uveitis was induced in two monkeys by immunization with IRBP and serial fluorescein angiograms performed using different sized dextrans linked to fluorescein. The aim of these studies is to provide data on the retinal vessels and toxicology data to enable these agents to be used in humans. We have demonstrated that the larger molecular weight dextrans are less permeable than sodium fluorescein in the inflamed retina.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00230-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Quantitative Assessment of Retinal Vascular Permeability

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Susan Lightman	M.D.	Visiting Fellow	LI, NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI

COOPERATING UNITS *(if any)*
Laboratory of Neurosciences, National Institute on Aging (Emanuel Rechthand, M.D.); Laboratory of Neurosciences, National Institute on Aging (Stanley Rapoport, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.08	0.08	0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A sensitive quantitative method was set up for examining the permeability of retinal vessels in the rat. Baseline values for normal rat retinal vessels were established and the method will be applied to pathological situations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00217-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Lymphocyte Migration in Experimental Autoimmune Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
	Consuelo Muellenberg-Coulombre		Chemist	LI, NEI
	Myung Kim	M.D.	Visiting Fellow	LI, NEI
	Susan Lightman	M.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.3	0.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Experimental autoimmune uveitis (EAU) is induced by immunization of rats and other experimental animals with S-antigens (a soluble antigen from the retina) is being investigated in this laboratory as a model of human intra-ocular inflammation. This experimental inflammation can be transferred from donor rats to naive recipients using lymphocytes harvested from the spleen or lymph nodes. Following harvesting of the cells from the donors and three days in culture with stimulating antigen, the cells are injected into the intra-peritoneal cavity and five to seven days later the recipient rats develop EAU. The disease can also be transferred using a T-helper cell line by intra-peritoneal or intra-ocular injection. The mechanism of transfer of disease is unclear. This work has used radioactively labeled lymphocytes to determine the fate of these lymphocytes after injection into the peritoneal cavity or blood during the process of the development of uveitis. The goal of this project is to understand the initiating mechanisms of inflammation in the hope that these mechanisms can be extended and applied to human inflammations. Thus far we have determined that only a small percentage of the lymph node lymphocytes injected into the peritoneal cavity actually reach the eye during the induction of EAU. Of 100 million cells transferred into the peritoneal cavity, approximately 5,000 reach the eye. Many more reach the spleen, liver and thymus however. The work is now being extended to study the migration patterns of intra-peritoneal or intra-ocular T-cell lines.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00218-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Human T-cell Leukemia/Lymphotropic Virus Type III and Eye Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	LI, NEI
-	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
	Myung Kim	M.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)* Laboratory of Tumor Cell Biology, National Cancer Institute (S. Zaki Salahuddin, Ph.D.); Laboratory of Cellular & Molecular Biology, National Cancer Institute (Dharam Ablashi, D.V.M.); Department of Critical Care Medicine, Clinical Center (Henry Masur, M.D.); Laboratory of Tumor Cell Biology, National Cancer Institute (Robert C. Gallo, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.91	0.91	0

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

HTLV-III was studied in ocular fluids and cells in order to characterize its possible involvement in ophthalmic disease in AIDS and possible transmissibility through ocular fluids.

a. HTLV-III was isolated from the tear fluid of patients with AIDS by using Schirmer's filter paper strips and infection of lymphocytes plus retransmission to other lymphocytes.

b. Studies indicate that conjunctival epithelial cells from AIDS patients contain HTLV-III and may therefore serve as a reservoir for the virus.

c. Further studies suggest more widespread presence of HTLV-III in ocular tissue such as the cornea and vitreous.

Patients with AIDS and cytomegalovirus retinitis were studied to improve therapy for this blinding disorder. Laser therapy for active lesions was ineffective, but the antiviral drug DHPG was effective in treating but not curing the infection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00219-01 LI

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Effect of Bromocriptine on Human Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Consuelo Muellenberg-Coulombre		Chemist	LI, NEI
	Myung Kim	M.D.	Visiting Fellow	LI, NEI
	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI

COOPERATING UNITS *(if any)*

Metabolism Branch, National Cancer Institute (Marie C. Gelato, M.D.)

LAB/BRANCH

Laboratory of Immunology

SECTION

Section on Clinical Immunology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER
0.29	0.29	0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In recent years there has been increasing evidence in the literature that pituitary hormones are capable of regulating the immune system. There is evidence to suggest that prolactin is an immunostimulatory hormone and that reduction of serum prolactin levels in experimental animals by hypothesectomy or bromocriptine will result in a degree of immunosuppression.

This information has been applied to humans and two clinical studies have begun. Both of these are in early phase of patient recruitment. One study is a randomized trial between placebo and bromocriptine in recurrent anterior uveitis using the end point of the number of recurrences per year to determine whether or not bromocriptine is capable of regulating the immune system in these patients. The second trial focuses on the additive effects of cyclosporine plus bromocriptine in attempts to treat patients with posterior uveitis at lower doses of cyclosporine in order to reduce its concurrent renal toxicity while at the same time achieving an immunosuppressive effect. Cyclosporine and prolactin compete for binding sites on the lymphocyte.

Further studies in human disease will hopefully elucidate other aspects of the neuroendocrine axis which can be utilized to regulate the immune system to treat autoimmune diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00220-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Endocrine Modulation of Immune-Mediated Eye Disease in Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Consuelo Muellenberg-Coulombre		Chemist	LI, NEI
	Myung Kim	M.D.	Visiting Fellow	LI, NEI
	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI

COOPERATING UNITS *(if any)*
Metabolism Branch, National Cancer Institute (Marie C. Gelato, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.89	0.89	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In recent years there has been increasing evidence in the literature that pituitary hormones are capable of regulating the immune system. There is evidence to suggest that prolactin is an immunostimulatory hormone and that reduction of serum prolactin levels in experimental animals by hypothesectomy or bromocriptine will result in a degree of immunosuppression.

An animal model of experimental autoimmune uveitis (EAU) induced by immunization of rats with S-antigen (a soluble antigen from the retina) is used as a model for intraocular inflammatory disease. We have demonstrated that concurrent antibody production in both males and females and the incidence of uveitis in female animals but did not have a significant effect on the immune responses measured by lymphocyte proliferation. As reported before, cyclosporine in high doses (10 mg/kg) there is only partial effect. We have demonstrated that the concurrent use of bromocriptine to suppress prolactin in combination with low dose cyclosporine is more effective than either drug separately in suppressing both the incidence of disease as well as the cellular and humoral immune responses to immunization. There is evidence in the literature to suggest that cyclosporine is able to compete for binding on the lymphocyte by prolactin and that reductions in prolactin level may therefore make cyclosporine more effective. Further studies in animal disease will hopefully elucidate other aspects of the neuroendocrine axis which can be utilized to regulate the immune system to treat autoimmune diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00221-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Intraocular Class II Antigen Expression in Endotoxin-Induced Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Myung Kim	M.D.	Visiting Fellow	LI, NEI
	Consuelo Muellenberg-Coulombre		Chemist	LI, NEI
	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.51	0.51	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Endotoxin is a polysaccharide derived from the cell wall of gram negative bacteria. When injected into the footpad or the eye of a rat it will induce an inflammatory reaction within the eye. Endotoxin injection in the footpad does not lead to inflammation in other organs but does produce bilateral uveitis primarily centered at the ciliary body and iris. The mechanism of this inflammation is still unclear. However, since several types of anterior uveitis in humans appear to be linked to gram negative bacteria exposure, this is considered a relative model for anterior uveitis in humans such as Reiter's syndrome. In this study rats received E. coli endotoxin and the expression of class II antigens was studied within the eye using immunohistochemical techniques. We observed that the expression of class II antigens on the ciliary body and iris preceeded the influx of inflammtory cells into the eye and that the inflammatory cells that entered the eye were primarily neutrophils with some monocytes. No T-cells were present in the inflammatory infiltrate. The expression of class II antigens within the eye was restricted to the iris and ciliary body during this inflammatory episode and did not involve the retinal pigment epithelium or retinal vessels. The inflammatory cellular infiltrate could be inhibited by indomethacin or colchicine, however this did not alter the expression of class II antigens by the iris or ciliary body indicating that this expression is not simply a consequence of the inflammatory infiltrate but may be intimately involved with the mechanism of the expression of endotoxin induced uveitis. Corticosteroids were capable of suppressing both the cellular inflammatory infiltrate and the expression of class II antigens. The expression of class II antigens on nonlymphoid cells within the eye may be important in antigen presentation or may simply signal a phenotypic change on the cells due to the interaction of endotoxin with the cell membranes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00231-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cell Surface Antigens on Retinoblastoma Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Barbara Detrick	Ph.D.	Expert	LI, NEI
Others:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
	Gerald J. Chader	Ph.D.	Chief	LVR, NEI
	Merlyn Rodrigues	M.D., Ph.D.	Head, Section on Clinical Eye Pathology	LOP, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI

COOPERATING UNITS *(if any)*
Duke University, Durham, North Carolina (Barton F. Haynes, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Experimental Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.75	0.75	0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☒ (b) Human tissues
- ☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Class II antigens (HLA-DR and HLA-DQ) are membrane bound glycoproteins encoded by genes in the major histocompatibility complex. In addition to their well established role as regulatory molecules of the immune response, these determinants are now suspected of playing an influencial part in cellular differentiation.

In exploring the cellular composition of a popular childhood tumor, retinoblastoma, we have had an opportunity to describe class II antigens on a population of undifferentiated malignant cells of the retina. This study provides the initial description of class II antigens on retinoblastoma cells. Furthermore, HLA-DR antigen was found to be coexpressed on cells that contained both neuronal and glial markers. This study also identifies for the first time the presence of class II antigens on cells of neuronal origin.

Based on these initial studies, two areas will be explored. The first approach will focus on the possible role of class II antigens in the cellular differentiation or immune reactivity. The second will examine the prognostic significance of these molecules on retinoblastoma cells and the possible relationship class II proteins may have to the modulation and management of this tumor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00235-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Identification and Modulation of Class II Antigens

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Barbara Detrick	Ph.D.	Expert	LI, NEI
Others:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	Leslie Fujikawa	M.D.	Senior Staff Fellow	LI, NEI
	Richard Wetzig	M.D.	Senior Staff Fellow	LI, NEI
	Caroline Percopo	A.B.	Biologist	LI, NEI

COOPERATING UNITS (if any) Eye and Ear Infirmary, University of Illinois, Chicago, Illinois (M.O.M. Tso, M.D.); Duke University, Durham, North Carolina (Barton F. Haynes, M.D.); Paris, France (Laurence Boumsell, M.D.): and Paris, France (Alain Bernard, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Experimental Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.6	0.5	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Class II antigens are membrane bound glycoproteins that are encoded by genes in the mixed histocompatibility complex (MHC). The expression of these antigens allows a cell to participate in the initiation and perpetuation of immune responses. Furthermore, although most cells that constitutively express class II antigens are members of the immune system, other cell types can be induced to demonstrate these molecules under selected conditions, such as an immunologic or degenerative event. Early investigations demonstrated that patients with the retinal degenerative disorder retinitis pigmentosa had a unique alteration in two regulatory proteins, interferon-gamma and the MHC class II antigen, HLA-DR. In addition, in vitro studies revealed that a regulatory cell in the eye, the rpe cell, could also express this antigen and that these determinants were sensitive to modulation with interferon-gamma. Based on these findings we expanded our studies to evaluate class II antigen expression in ocular diseases. We found that the rpe cell does not express class II antigen in the normal eye. In contrast, the rpe cell did express these molecules in a retinal degenerative disorder (retinitis pigmentosa) and in two ocular inflammatory diseases (sympathetic ophthalmia and uveitis). Using the EAU animal model of ocular autoimmune disease we demonstrated that the rpe cell is activated to express class II antigens prior to clinical and histopathological evidence of the disease. We are now evaluating the effects of such modulators as interferon-gamma, anti-Ia antiserum and cyclosporine on class II antigen expression with the hope that an alteration in activation or expression of these molecules may modify the disease process to the benefit of the host.
In summary, these studies indicate that the appearance and modulation of class II antigens may play a role in the initiation, maintenance or regulation of pathologic events in degenerative or inflammatory processes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00069-09 LI

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Immune Responses to Ocular Antigens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LI, NEI
Others:	Shigeto Hirose	M.D.	Visiting Fellow	LI, NEI
	Cathy McAllister	Ph.D.	Extramural Fellow	LI, NEI
	Barbara Vistica	B.A.	Microbiologist	LI, NEI
	Gregory Fox	B.A.	HHMI-NIH Research Scholar	LI, NEI

COOPERATING UNITS *(if any)*: Tokyo Medical College Hospital, Tokyo, Japan (Dr. M. Usui)

LAB/BRANCH: Laboratory of Immunology

SECTION: Section on Experimental Immunology

INSTITUTE AND LOCATION: NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.7	2.1	0.6

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is aimed at learning about the pathogenesis of immune-mediated eye diseases, mainly by investigating the animal disease, "experimental autoimmune uveitis" (EAU), which is induced in various animals by immunization with certain eye components. EAU is considered a model for certain human ocular conditions. Research during FY 1986 has focused on EAU induced by interphotoreceptor retinoid-binding protein (IRBP). Our previous study (FY-1985) showed that IRBP is highly uveitogenic in Lewis rats. Major new findings include: (1) Rats of different inbred strains vary in their susceptibility to EAU induced by IRBP or by another retinal protein, S-antigen (S-Ag). This finding shows that the susceptibility to EAU is related to genetic makeup and supports the assumption that the susceptibility to immune-mediated diseases in man is also genetically regulated. (2) The pathogenic mechanism of IRBP-induced EAU was found to be cell mediated: the disease could be adoptively transferred by lymphocytes and a correlation was found between EAU development and cellular immunity but not with antibody production. (3) Monkey IRBP was found to be 20 times less uveitogenic in rats than bovine IRBP. The two IRBPs showed cross reactivity when used for stimulation of lymphocytes for EAU induction, but did not cross react by the lymphocyte proliferation assay. This finding indicates that lymphocyte responses in vitro do not necessarily represent their capacity to induce disease in vivo. (4) Monkeys were found highly susceptible to IRBP-induced EAU. This monkey disease is of special interest by showing a close similarity to certain ocular diseases in man, in particular sympathetic ophthalmia and Vogt-Koyanagi-Harada disease. Similarly to these human diseases, IRBP-induced in monkey was expressed mainly as granulomatous choroiditis. In addition to providing a useful model for the human diseases, the findings with IRBP-induced EAU in monkeys support the notion that autoimmune processes to retinal antigens participate in the etiology of certain human eye diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 0023-08 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Macrophage and Lymphocyte Participation in Inflammatory Processes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LI, NEI
Others:	Cathy McAllister	Ph.D.	Extramural Fellow	LI, NEI
	Barbara Vistica	B.A.	Microbiologist	LI, NEI

COOPERATING UNITS *(if any)*
Laboratory of Developmental and Molecular Immunity, National Institute of Child Health and Human Development (R. Sekura)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Experimental Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.1		0.1

CHECK APPROPRIATE BOX(ES)
- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☒ (b) Human tissues
- ☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been aimed at collecting information concerning the processes which bring about inflammation and the involvement of lymphocytes, macrophages and immune mediators in these processes. Experiments carried out this year have further examined the effects of pertussis toxin (PT) on lymphoid cells in culture. This bacterial product is a powerful adjuvant and it facilitates remarkably the induction of experimental autoimmune diseases. Our previous experiments (FY 1985) have shown that PT stimulates lymphocytes and macrophages in culture. Experiments carried out this year have indicated that PT has a dual effect on these lymphoid cells. Thus, cultures of lymphocytes or macrophages which are stimulated by other agents are often inhibited by the addition of PT at doses which are simulatory to cultures with no other stimuli. This finding is in line with reports showing that, at certain circumstances, PT may both enhance and inhibit immune responses.

This project is being phased out, in order to focus the Section's effort on issues which relate directly to the immunopathogenesis of ocular inflammatory diseases (see project # 201 EY 00069-09).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00232-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Interferon System in Cellular Function and Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	A.B.	Biologist	LI, NEI
	Yotanna Dalavanga	M.D.	Visiting Fellow	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI

COOPERATING UNITS *(if any)*
New York University, School of Medicine, Department of Microbiology (Jan Vilcek, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunology and Virology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:
1.45	0.75	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The IFN proteins can modify a variety of biological activities and are considered one of the body's regulatory proteins. Numerous studies now indicate that the IFN's are potent immunoregulators. During the past year we have been studying the ways in which IFN proteins interact with cells of the immune system and how this interaction may modify immune responses and immunologically related disorders.

Using immunocytochemical analysis we have developed a sensitive method of identifying lymphokines, IFN-gamma and IL2, at the site of tissue damage. We have identified the lymphokines, IFN-gamma and IL2 in inflammatory eye diseases. The presence of these lymphokines is associated with a lymphocyte infiltrate predominantly of a T-cell origin and with the expression of MHC class II antigens on both the infiltrating cells and in the retinal pigment epithelial (rpe) cells.

This is the first demonstration of lymphokines, IFN-gamma and Il2 at the site of a localized autoimmune disease. These observations may indicate that IFN-gamma induced MHC class II antigen expression may serve as a local amplification system in autoimmune and inflammatory eye disease. A better understanding of the role of lymphokines in the mechanisms involved in the development of autoimmunity and inflammation may be beneficial in the treatment of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00232-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Interferon System in Cellular Function and Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others;	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	A.B.	Biologist	LI, NEI
	Yotanna Dalavanga	M.D.	Visiting Fellow	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI

COOPERATING UNITS *(if any)*
New York University, School of Medicine, Department of Microbiology (Jan Vilcek, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunology and Virology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.45	0.75	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The IFN proteins can modify a variety of biological activities and are considered one of the body's regulatory proteins. Numerous studies now indicate that the IFN's are potent immunoregulators. During the past year we have been studying the ways in which IFN proteins interact with cells of the immune system and how this interaction may modify immune responses and immunologically related disorders.

Using immunocytochemical analysis we have developed a sensitive method of identifying lymphokines, IFN-gamma and IL2, at the site of tissue damage. We have identified the lymphokines, IFN-gamma and IL2 in inflammatory eye diseases. The presence of these lymphokines is associated with a lymphocyte infiltrate predominantly of a T-cell origin and with the expression of MHC class II antigens on both the infiltrating cells and in the retinal pigment epithelial (rpe) cells.

This is the first demonstration of lymphokines, IFN-gamma and Il2 at the site of a localized autoimmune disease. These observations may indicate that IFN-gamma induced MHC class II antigen expression may serve as a local amplification system in autoimmune and inflammatory eye disease. A better understanding of the role of lymphokines in the mechanisms involved in the development of autoimmunity and inflammation may be beneficial in the treatment of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00233-01 LI

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(60 characters or less. Title must fit on one line between the borders.)*

Studies on the Bioregulatory Aspects of the Retinal Pigment Epithelial Cell

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)*

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	A.B.	Biologist	LI, NEI
	Yotanna Dalavanga	M.D.	Visiting Fellow	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	Garth Stevens, Jr.	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

National Institute of Dental Research, Clinical Immunology Section (Siraganian Reuben, M.D.)

LAB/BRANCH

Laboratory of Immunology

SECTION

Section on Immunology and Virology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.4	1.1	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The retinal pigment epithelial (rpe) cell is a major regulatory cell in the eye. That is, the rpe cell exerts a variety of actions in maintaining retinal integrity and function. In order to more effectively study this cell in vivo and in vitro, we have produced monoclonal antibodies directed against human rpe cells.

Using immunoperoxidase assays (ABC), we have identified two mouse IgG monoclonal antibodies which react with the human rpe cell. The monoclonal antibodies are both specific for the rpe cell within the eye, since they do not react with any other ocular structures. Moreover, these antibodies do not cross react with human skin, kidney or peripheral mononuclear cells.

This is the first monoclonal antibody which is directed solely at the human rpe cell. Further characterization and studies with this antibody should prove useful in the identification of rpe cells in situ and in vitro. Moreover, this immunoglobulin will allow us to probe the bioregulatory functions of the cell.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00234-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
MHC Class II Antigens in the Pathogenesis of Inflammatory Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Yotanna Dalavanga	M.D.	Visiting Fellow	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI

COOPERATING UNITS *(if any)*
Ioannina School of Medicine, Ioannina, Greece (Haralampos M. Moulsopoulos, M.D.)

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunology and Virology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.56	0.56	0

CHECK APPROPRIATE BOX(ES)
- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

MHC class II antigens, HLA-DR in the human and Ia in the mouse, are membrane bound glycoproteins that are encoded by genes of the major histocompatibility complex. Expression of these antigens is of great functional importance for the initiation and perpetuation of immune responses. In a number of immunopathologic conditions HLA-DR antigen negative cells are stimulated to express class II antigens. In these cases an immunologic role has been postulated for the class II antigen expression.

During the past year, we have determined if class II antigens are expressed in certain diseases and we have evaluated their possible role in autoimmune and inflammatory diseases. Initial studies identified cells in the anterior segment and cells in the retina (rpe cell) which express class II antigens during inflammatory eye diseases. These studies have been extended to evaluate Sjogren's syndrome. We found that the salivary gland in Sjogren's syndrome is infiltrated predominantly by T-lymphocytes and that this is associated with class II antigen expression on glandular epithelial cells.

These studies on MHC class II antigen expression in localized autoimmune diseases provide evidence that the activation of these antigens may contribute to the immunopathogenesis of these disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00184-04 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cellular Mechanisms in Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Rachel Caspi	Ph.D.	Visiting Fellow	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
	Francois Roberge	M.D.	Visiting Associate	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI
	Susan Lightman	M.D.	Visiting Fellow	LI, NEI
	Myung Kim	M.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)*

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TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.02	1.02	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In vivo functional long-term T-cell lines and T-cell clones are developed and maintained in vitro from both peripheral blood and ocular fluids of humans and animals. The phenotype and functional properties of these cells, as well as their interaction with ocular resident cells are being studied. The goal of these studies will be to identify the immunoreactive cells and mediators involved in the intraocular inflammatory process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00222-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Kinetics of T-lymphocytes in the Eyes with Experimental Autoimmune Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
Others:	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LI, NEI
	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI

COOPERATING UNITS *(if any)*
University of Tokyo, School of Medicine (Manabu Mochizuki, M.D.); Hadassah Hebrew University Hospital, Department of Ophthalmology (David BenEzra, M.D.)

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TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:
0.07	0.07	0

CHECK APPROPRIATE BOX(ES)
- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Identity and topographic localization of immunocompetent cells in rats with experimental autoimmune uveoretinitis were analyzed by immunohistochemical studies. The lymphocyte population at the inflammatory sites was found to change markedly during the course of disease. In the early stage, T-helper/inducers are the predominant cells in the eye. A relative increase of T-suppressor/cytotoxic cells in the late stage were observed. These kinetics can be influenced by cyclosporine and dexamethosone treatment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00223-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Expression of Class II Antigens in Ocular Inflammatory Disorders

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	LI, NEI
	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LI, NEI

COOPERATING UNITS (if any)

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.3	0.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Expression of class II antigens on ocular nonlymphoid cells was evaluated in experimental autoimmune uveoretinitis (EAU) by the immunoperoxidase technique. Class II antigens on nonlymphoid cells were not detected from normal rats. However, these antigens were detected on the retinal pigment epithelia and ciliary body epithelia a few days prior to the development of clinical and histopathological EAU. Ia antigen was noted on the retinal vascular endothelia at the onset of cellular infiltration in the retina, and appeared on the corneal keratocytes and scleral fibroblasts after the early stage of clinical EAU.

The study demonstrates that during the course of EAU the ocular nonlymphoid cells can be activated to express class II antigens. This antigen expression may be important in the initiation and perpetuation of immune reactivity in the eye.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00224-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Sympathetic Ophthalmia: Immunopathological Findings

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	LI, NEI
	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Garth Stevens, Jr.	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.37	0.37	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Immunocompetent cells in the ocular tissues from six patients with a clinical diagnosis of sympathetic ophthalmia were examined using the immunohistochemical technique. The choroidal infiltrates were composed primarily of T-lymphocytes. Different amounts of macrophages and 13 lymphocytes were present in each case. A varied spectrum of immunopathological and histopathological findings may occur in clinically diagnosed sympathetic ophthalmia.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00225-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Post-Inflammatory Complications in Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	LI, NEI
	Richard P. Wetzig	M.D.	Senior Staff Fellow	LI, NEI
	Francois Roberge	M.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

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TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.19	0.19	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Complications of post-inflammation in uveitis patients included destruction of photoreceptors, gliosis, choroidal scar, and formations of cyclitic membrane, snowbanking and preretinal membrane. Eyes enucleated from patients with end stages of chronic anterior uveitis (formation of cyclitic membrane), pars planitis (formation of preretinal membrane) were evaluated. Glial cells and proliferating Muller cells were the major components in these membranes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00226-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Immunopathology of Ocular Onchocerciasis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI

COOPERATING UNITS *(if any)*
National Institute of Allergy and Infectious Diseases, Clinical Parasitic Diseases Section (Eric A. Ottesen, M.D.)

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.2	0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☒ (b) Human tissues
- ☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ocular specimens and sera from 12 patients with onchocerciasis and 10 controls were studied. A mild to moderate chronic inflammatory cellular infiltration was present in the conjunctiva of the onchocerciasis patients. T-lymphocytes were the predominant inflammatory cells with the T-suppressor subset being significantly increased in the onchocerciasis patients when compared to controls. In the onchocerciasis patients, the nonlymphoid cells in the conjunctiva and iris, such as vascular endothelia, pericytes and fibroblasts, showed an increase in expression of class II antigens. The anti-onchocerca Volvulus antibodies in the sera and aqueous humor were significantly higher in the patients compared to the controls. These findings suggest that T-cells are important in the ocular immune response to onchocerca and that expression of class II antigens on nonlymphoid cells and the humoral factors may all play a critical role in ocular onchocerciasis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00216-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Role of Fibronectin in Wound Healing in the Eye

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
	Manuel Datiles	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

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TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.18	0.18	0

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The role of fibronectin in corneal wound healing was studied both in man and in experimental animals. Studies were carried out in order to characterize the possible effect of fibronectin on facilitating wound healing of the epithelium in rabbits. A randomized masked study will evaluate the effectiveness of fibronectin drops in treating recurrent corneal epithelial defects in patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00092-08 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
HLA, ABO, and B-cell Alloantigens and Ocular Inflammatory Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: Robert B. Nussenblatt M.D. Deputy Clinical Director NEI

COOPERATING UNITS *(if any)*

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.03	0.03	0

CHECK APPROPRIATE BOX(ES)
- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with ocular toxoplasmosis, pars planitis, Behcet's disease, chorioretinitis of unknown origin, are being studied to determine the phenotype frequency of the HLA, ABO, and B-cell alloantigens. Because the B-cell alloantigens or DR antigens are thought to play a role in the immunologic response to antigens, these findings will complement other immune uveitis studies being simultaneously carried out.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00075-08 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Immune Functions in Ocular Diseases of Obscure Etiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI
	Shigeto Hirose	M.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)*

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INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.86	0.26	0.6

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In vitro cellular immune functions and lymphocyte subsets are being studied in a masked method in patients with ocular toxoplasmosis, pars planitis, Behcet's disease, geographic choroiditis, and chorioretinitis of unknown origin. Crude ocular antigens, as well as purified uveitogenic soluble antigen (S-antigen) and IRBP of the retina, are being used in a lymphocyte microculture technique to evaluate the presence of cellular immune memory to ocular tissues. In addition, purified antigens from the toxoplasmosis organism are also being tested in this in vitro system. A subgroup of patients with posterior uveitis has been identified as having this immunologic memory. Lymphocyte subsets in the blood and in the eye are being defined in these patients by monoclonal antibodies. These results shed light on the basic mechanisms of uveitis and may be used as a guide for specific immunologic therapy. In a small group of selected patients, chorioretinal biopsies are performed to evaluate the on-going ocular immune response.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00094-08 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Immune Mechanisms in Experimental Autoimmune Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
Others:	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LI, NEI
	Cathy McAllister	Ph.D.	Extramural Fellow	LI, NEI
	Barbara Vistica	B.A.	Microbiologist	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*

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INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.75	0.35	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Lewis rats and non-human primates, immunized at a site distant to the eye with the retinal soluble antigen (S-antigen) in complete Freund's adjuvant, develop experimental autoimmune uveitis (EAU). Lymph node cells and peripheral lymphocytes from immunized animals manifested significant cellular immune responses measured by the lymphocyte culturing technique. Cyclosporine, a drug with specific anti-T-activity, has been found to be exceptionally effective in protecting rats with EAU, and suppressor cells potentially play a role in this protective mechanism. As well, the inducer cell T-cell fraction in the lymph node appears to be most susceptible to cyclosporine therapy. Attempts at local immunosuppressive therapy in order to prevent EAU have begun. The use of topical CsA has been used to evaluate its effectiveness in EAU. Additionally, newer cyclosporines, particularly D&G, have been evaluated in this model, with their efficacy compared to that of cyclosporine A. Ciamexone, a drug with immunopotentiating characteristics, has always been utilized in this model.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 00115-06 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cyclosporine Therapy in Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Garth Stevens, Jr.	M.D.	Senior Staff Fellow	LI, NEI
	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	LI, NEI
	Francois Roberge	M.D.	Visiting Associate	LI, NEI
	Richard P. Wetzig	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.52	2.52	0

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cyclosporine, an endecapeptide fungal product with specific anti-T-cell characteristics, will be administered to patients with sight-threatening ocular inflammatory disease of non-infectious origin who have failed on either corticosteroid or cytotoxic agent therapy. This will be done to test cyclosporine's efficacy in the treatment of uveitis. Within the context of these ongoing studies, the effect of hydergine on reversing cyclosporine induced nephrotoxicity is being evaluated in a randomized, masked, cross-over study. Additionally, selected patients whose uveitis is well controlled on cyclosporine for one year or more are undergoing kidney biopsies to evaluate the long term effects of this agent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00159-04 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cyclosporine Therapy of Childhood Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)*

PI:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*

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Section on Immunoregulation

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.15	0.05

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The efficacy of cyclosporine, an endecepeptide with specific anti-T-cell characteristics, is being tested in children with sight-threatening ocular inflammatory disease of non-infectious origin who have failed on conventional therapy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00215-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Randomized Double-Masked Study of Cyclosporine in Treating Endogenous Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Garth Stevens, Jr.	M.D.	Senior Staff Fellow	LI, NEI
	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	LI, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	Richard P. Wetzig	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

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TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.6	0.6	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cyclosporine's efficacy in the treatment of severe endogenous uveitis was evaluated in this randomized, double-masked study. The study will evaluate the effectiveness of cyclosporine therapy to that of systemic corticosteroid administration. Patients meeting the entry requirements were randomized to either cyclosporine or corticosteroid therapy. Patients are evaluated at three months in order to determine whether they were therapeutic "successes" or not. If not, the patients are then treated with the alternate medication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00228-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Study of Ocular Glial Cells Involvement in Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Francois Roberge	M.D.	Visiting Fellow	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	Rachel Caspi	Ph.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.06	1.06	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The work concerns uveoretinal inflammatory disease mechanisms. The study focused on evaluating the role of resident cells at the target organ level. Muller cells interactions with T-lymphocyte cell line was studied in vitro. Two opposite effects of Muller cells on T-lymphocytes proliferation were found that could be expressed under different culture conditions. An inhibitory effect on antigen driven proliferation of T-helper lymphocytes could be modulated with various drugs that allowed the Muller cells to function as antigen presenting cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00227-01 LI

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Histopathology of Pars Planitis and Experimental Autoimmune Uveitis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Richard P. Wetzig	M.D.	Senior Staff Fellow	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Deputy Clinical Director	NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	LI, NEI
	Barbara Detrick	Ph.D.	Expert	LI, NEI
	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER
0.67	0.67	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies in animals and in patients are being carried out to determine factors influencing ocular immune responses. In an animal model, rats are immunized with S-retinal antigen to produce experimental autoimmune uveitis. Animals in one group received anti-Ia antibody intraperitoneally and developed the onset of uveitis significantly later and to a lesser extent than controls. Histopathologically, the anti-Ia treated animals had much less inflammation than did controls. A human eye with pars planitis was also studied immunohistologically. In the pars plana region there was an elevated helper to suppressor T-cell ratio. In addition, the snowbank area showed staining for glial fibrillary acid protein Muller cells, type IV collagen and laminin. There was staining for HLA-DR throughout the globe. The results of these studies shed light on how surface antigens effect and are transmitted by ocular immune responses.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00201-02 LMOD

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Biology of Aldose Reductase

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Deborah Carper	Ph.D.	Biologist	LMOD, NEI
Others:	Toshimichi Shinohara	Ph.D.	Biologist	LMDB, NEI
	Cheryl Craft	Ph.D.	Guest Worker	MIDP, NICHHD
	Jin H. Kinoshita	Ph.D.	Scientific Director	NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Mechanisms of Ocular Disease

SECTION
Section on Cataracts

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Aldose reductase (AR), an enzyme which converts sugars to sugar alcohols, has been implicated in diabetic complications of the eye and the peripheral nerves. Our studies have focused on isolating and characterizing the gene for aldose reductase. As an initial step, putative AR cDNA clones from a bovine retina cDNA λgt 11 library were isolated and sequenced. Sequencing of three non-homologous inserts yielded approximately 700 nucleotides or around one-third of the full length mRNA. Northern analysis showed that the full size of AR mRNA is around 2 kilobases in the bovine retina and slightly larger in the bovine brain. Homologies between the bovine retina AR cDNA and mRNAs from cultured dog lens epithelial cells and cultured rabbit kidney cells have not been detected. Restriction enzyme analysis of total bovine genomic DNA indicates that fewer than 3 genes are present.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00236-01 LMOD

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Philly Mouse Cataract

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Deborah Carper	Ph.D.	Biologist	LMOD, NEI
Others:	George Inana	M.D., Ph.D.	Medical Officer	LMOD, NEI
	Jin H. Kinoshita	Ph.D.	Scientific Director	NEI

COOPERATING UNITS *(if any)*

John Clark Ph.D., faculty University of Washington School of Medicine
Mike Gorin M.D., Ph.D. UCLA School of Medicine

LAB/BRANCH

Laboratory of Mechanisms of Ocular Disease

SECTION

Section on Cataracts

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies are continuing on the Philly mouse which develops a dominantly inherited cataract. The cataract is visible by 35 days of age. Microscopic changes in the lens occur much earlier and include failure of lens fiber cells to elongate. We have been investigating several facets of cataract development in the Philly mouse including the composition of crystallin proteins at different stages in lens growth, synthesis and translational efficiencies of lens mRNAs, and phase transition temperatures in the Philly mouse and F_1 heterozygote.

2-D gel electrophoresis of Philly mouse lens proteins indicate a specific deficiency of a 27K basic β-crystallin and its functional mRNA. Interestingly, a unique more acidic 26K protein and its functional mRNA is present. The relationship between these two proteins is now being investigated using a βB_p cDNA probe.

The behavior of the lens cytoplasm phase transition temperature (Tc) was different in the Swiss-Webster, Philly, and Swiss Webster x Philly heterozygotes. The slope (dTc/dt) changes from negative to positive on day 27 for the Philly and day 38 for the hybrid, just prior to cataract in these animals. The slope continues to be negative in the Swiss Webster. The change in slope is a graphical confirmation of the disturbance in lens cell composition and an early indicator of conditions which lead to opacity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00189-03 LMOD

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Protein Kinases in Lens Function and Oxidation of Proteins in Cataractogenesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Donita L. Garland Ph.D Expert LMOD, NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Mechanisms of Ocular Disease

SECTION
Section on Cataracts

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The role of protein kinases in regulating metabolism in lens is being addressed by studying: 1) the protein kinases, and 2) the endogenous proteins that serve as substrates for the lens protein kinases. The focus of this study is on the purification of the protein kinases and the characterization of the phosphorylation of four endogenous substrates by cAMP-dependent protein kinases. The phosphorylated proteins are α-crystallin and 26K and 19K intrinsic membrane proteins. Comparison of the amino acid compositions of the 26K and 19K proteins suggest they are closely related. Detailed structural studies are in progress to determine how similar they are. Compounds that are thought to regulate the function of the 26K protein in vivo modulate the phosphorylation of the protein in vitro.

Oxidative changes of lens proteins are thought to occur with aging and to contribute to the development of cataracts. The goals of this project are to determine: 1) the extent of oxidative modification of crystallins and metabolic enzymes in both normal and cataractous lenses; 2) the nature of the modifications and mechanisms leading to the changes; 3) the effect of the modifications on structure and function of lens protein. Bovine and human lenses were used. Incubation of crystallins with ascorbate - $FeCl_3$-O_2 caused nondisulfide crosslinking of α and β and the partial degradation of all 3 crystallin fractions. Conversion to more acidic species occurred with all 3 fractions, and nontryptophan fluorescence was produced in β_H fraction. Longer incubations of homogenate with ascorbate - Fe-O_2 mimicked changes similar to those in brunescent lenses. Proteins became brownish, insoluble and there was an increased carbonyl content.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00237-01 LMOD

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Characterization of the Primate Lens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Paul Russell Ph.D. Research Chemist LMOD, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Cataracts

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Developmental differences in the composition of lens proteins have been observed with both monkey and human lenses. These alterations in composition were similar to those observed in rodent lenses at similar stages in development. In order to investigate the role in which these changes may affect optical clarity, the lens crystallin proteins as well as the glycoproteins from the membrane of the lens cells have been studied. Differences in the crystallin composition may give an indication of factors involved in congenital cataracts. Changes in individual crystallins may also be important to understand the aging process in the lens.

β- and γ- crystallin compositions are changing in the early embryonic period of the primate lens. The β-crystallins have much higher apparent molecular weights in the fetal lens perhaps indicative of a different organization of the subunits of these proteins during this stage of development. In addition, the main γ-crystallin in the embryonic lens is only a very minor component in the adult lens. As the lens cells differentiate into fiber cells, the glycoprotein composition on their membranes changes. Specific glycoprotein differences have been seen in cataractous rodent lenses compared with normal lens; and using lectins, primate lenses can now be probed for changes related to cataract formation and development.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00105-07 LMOD

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Structure and Composition of Lens Crystallins with Respect to Cataractogenesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	J. Samuel Zigler, Jr.	Ph.D.	Research Biologist	LMOD, NEI
Others:	Valerie A. Lucas	Ph.D.	Visiting Fellow	LMOD, NEI
	Qing-ling Huang	M.D.	Visiting Fellow	LMOD, NEI

COOPERATING UNITS *(if any)*
Jules Stein Eye Institute, UCLA Medical School (J. Horwitz); Department of Chemistry, Adelphi University (F. Bettelheim); Department of Ophthalmology, University of Tennessee (H.M. Jernigan)

LAB/BRANCH
Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Cataract

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.8	2.8	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The ocular lens normally exists in an environment of high oxidative stress which is manifested in the occurrence of marked oxidative modification to lens proteins during aging and particularly during cataract development. We are engaged in characterizing such protein changes and elucidating the mechanisms which produce them. Model systems are used to study changes produced in organ cultured lenses or in crystallin solutions. Complex interactions among the various forms of activated oxygen are involved in the damage produced in such model systems and very probably in the lens in vivo as well. The potential of the various activated oxygen species to produce damage depends upon where they are generated, ie, inside the lens or in the external milieu. Understanding the interactions among the oxidant species and lens components is essential if we are to devise therapeutic means to prevent oxidative damage.

The study of animal colonies with hereditary cataract has provided numerous insights into processes of cataractogenesis. We have begun to investigate the nuclear cataracts present congenitally in a colony of guinea pigs. Dr. Q-L. Huang has isolated and described the crystallins from normal guinea pigs so that they can be compared with crystallins from the cataractous animals. The discovery of a new crystallin not present in other species raises exciting possibilities for study of gene expression in the lens.

Transport processes are vital to the maintenance of normal lens homeostasis. Dr. V.A. Lucas is studying the membrane protein present in lens which transports glucose across cell membranes. This glucose transporter has been isolated and an antibody raised against it. Characterization of glucose transport in monkey lens membranes has been done using specific binding assays and known inhibitors of the glucose transporter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00193-03 LMOD

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Biology of Hereditary Eye Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	George Inana	M.D., Ph.D.	Section Head	LMOD, NEI
Others:	Seiichi Totsuka	M.D., Ph.D.	Visiting Fellow	LMOD, NEI
	Carmelann Zintz	Ph.D.	Staff Fellow	LMOD, NEI
	Yoshihiro Hotta	M.D.	Visiting Fellow	LMOD, NEI
	T. Michael Redmond	Ph.D.	Staff Fellow	LRCMB, NEI

COOPERATING UNITS *(if any)*

See next page.

LAB/BRANCH
Laboratory of Mechanisms of Ocular Diseases

SECTION
Molecular Pathology Section

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.6	3.6	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ornithine Aminotransferase Deficiency in Gyrate Atrophy: Gyrate atrophy (GA) is an autosomal recessive degenerative disease of the retina and choroid of the eye which leads to blindness. We have isolated a gene probe for the human ornithine aminotransferase (OAT), a mitochondrial enzyme which is deficient in GA patients. The gene probe is a λgt11 cDNA clone which was obtained from our human cDNA library through a Western screening method using the anti-human OAT antibodies. The OAT cDNA is 2073 base pairs long and contains the complete coding sequence of the protein. The cDNA-derived OAT sequence is a precursor containing a leader sequence like other mitochondrial enzymes, matches the sequences of seven purified tryptic peptides of pure OAT, and shows homology with another mitochondrial enzyme, aspartate aminotransferase. Examination of the genomic organization of OAT using the cDNA as a probe revealed a gene family consisting of approximately four copies of OAT or OAT-like gene sequences. The OAT gene sequences were mapped to multiple chromosomal loci, confirming the presence of a gene family. Examination of the OAT genes of GA patients has revealed restriction fragment length polymorphisms but no grossly obvious abnormalities, including deletions. Characterizations of multiple gene clones of OAT and the status of OAT mRNA synthesis in GA patients are in progress.

Hereditary Retinoblastoma: We are investigating the molecular basis of malignant transformation in hereditary retinoblastoma using cell culture and molecular genetic techniques. To determine if retinoblastoma has a dominant or recessive malignant phenotype, retinoblastoma cells (Y79) were fused with non-malignant cells (NIH3T3), and the growth characteristics of the hybrid cells were studied. The hybrid cells, containing both the neomycin and GPT markers from the parents, are anchorage-dependent, have a fibroblastic morphology and do not grow in soft agar like the non-malignant parent. The results indicate the malignant phenotype of retinoblastoma to be recessive.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00003-14 LMOD

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pharmacology of Ocular Complications

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Peter F. Kador Ph.D. Research Chemist LMOD, NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Molecular Pharmacology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.3	2.8	0.5

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☒ (b) Human tissues
- ☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies are being conducted on events leading to the onset of various ocular diseases and on methods for their potential pharmacological control. The relationships between the enzymes aldose reductase and aldehyde reductase and the progression of ocular complications such as retinopathy, cataract, pupil function and iris changes, and keratopathy induced by diabetes or galactosemia are being investigated. Methods for either delaying or preventing the onset of these complications through the pharmacological control of aldose reductase are also being developed.

Events leading to the formation of several types of cataracts are also being studied as well as methods for controlling the onset of these cataracts through pharmacological intervention.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00149-13 LMOD

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Ultrastructure and Function of the Cells and Tissues of the Eye

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. Gerald Robison, Jr.	Ph.D.	Chief, Section on Pathophysiology	LMOD, NEI
Others:	Martin L. Katz	Ph.D.	Staff Fellow	LMOD, NEI
	Masao Nagata	M.D., Ph.D.	Visiting Associate	LMOD, NEI
	Thomas C. Hohman	Ph.D.	Senior Staff Fellow	LMOD, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Mechanisms of Ocular Diseases

SECTION
Section on Pathophysiology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
5.2	5.0	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Aldose reductase has been implicated in two histopathological hallmarks of diabetic retinopathy involving retinal capillary walls: 1) the selective loss in numbers of mural cells (intramural pericytes) from the capillaries; and 2) the thickening of the basement membranes which envelop the cells of the capillary walls. Mural cells contain aldose reductase, accumulate sorbitol, and appear to be more susceptible to incubation in high glucose than are endothelial cells. A thickening of capillary basement membrane ultrastructurally similar to that characteristic of diabetic retinopathy was induced in rat retinas by galactose feeding and was prevented by two structurally different inhibitors of aldose reductase. The diabetic-like thickening of retinal capillary basement membranes in galactose-fed rats was accompanied by other ultrastructural alterations mimicking changes typical of diabetic microangiopathy, such as multilamination, banding of collagen, and the formation of vacuoles and dense inclusions. Bovine, canine, and human mural cells and endothelial cells from retinal capillaries have been grown in cell culture so that the role of aldose reductase in basement membrane synthesis and in various complications of the diabetic state could be studied under chemically defined conditions. Aldose reductase inhibitors are useful for studies of the possible prevention of diabetic retinopathy by oral drugs.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1985 - September 30, 1986

REPORT OF THE CHIEF, LABORATORY OF MOLECULAR AND DEVELOPMENTAL BIOLOGY

Joram Piatigorsky, Ph.D.

This is the fifth year for the Laboratory of Molecular and Developmental Biology. The three Sections (established in FY 1986) have established autonomy while remaining integrated in their life-styles and their common efforts to study the visual system at the molecular level. The Thursday morning doughnut-data sessions have continued to keep everyone abreast of on-going work and use the collective knowledge of the laboratory members. The invited seminars on alternate Tuesdays was organized this year by Dr. Teresa Borras and featured a stimulating series of talks, while our journal club on the other Tuesdays continued to keep us informed on recent developments in this rapidly moving area of science.

Each Section made notable gains in their research this year, as indicated in the individual reports given in this volume. Some of the recent progress includes not just new findings but reflects a growing clarity in direction. For example, while my group continues to characterize the structure and organization of crystallin genes--ie, to clone and sequence--we have advanced our efforts to include function. Crystallin gene promoters are being studied simultaneously in cell-free systems, in cultured cells and in transgenic mice. Each approach has its advantages and pitfalls. By combining the methods we hope to active a deeper understanding of the regulated, tissue-specific nature of crystallin gene expression. Acquisition of an oligonucleotide synthesizer has also had an impact on our work in that we can now make mutations in cloned gene sequences more easily and cheaply. Despite the considerable expenses of this equipment, it has already paid for itself and been of use to several laboratories in the NEI and other institutes.

In addition to continuing to study the metabolic control of lens cell growth and differentiation, Dr. Peggy Zelenka's section has been increasingly incorporating molecular genetics in their work. Their initial finding reported last year that the oncogene mRNA c-myc is transiently increased during lens fiber cell differentiation has been developed and expanded to other oncogenes. They have found that several oncogenes are expressed in the developing lens, each with a characteristic pattern during differentiation. The role of the oncogene products in the lens is not known yet, but the combined approach of molecular and biochemical investigations should yield new insights to the regulation of lens cell growth and differentiation.

Last year Dr. Toshimichi Shinohara's group reported their initial studies on S-antigen of the retina. They identified several cDNA clones as S-antigen and begun in situ hybridization experiments on the localization of opsin and S-antigen mRNAs in the retina and pineal gland. This year Dr. Shinohara's group has obtained considerably more sequence information on S-antigen and isolated S-antigen genes from the mouse and human, opening new possibilities for the study of tissue-specific gene expression in the retina. Growing knowledge of the sequence of S-antigen has permitted the synthesis of peptides

of S-antigen. These, in turn, are being used to define sites of S-antigen which are responsible for the generation of uveitis in experimental rats. Thus, Dr. Shinohara's basic investigations are being productively coupled with studies having direct relevance to medicine.

In FY 1985 we began a very fruitful collaboration with Dr. Heiner Westphal and his colleagues in the Laboratory of Molecular Genetics (NICHD) for testing crystallin promoters in transgenic mice. These studies have now demonstrated the extreme tissue-specificity of the murine αA-crystallin promoter and its ability to regulate foreign genes (bacterial and viral) in transgenic mice. In one case, transgenic mice were made which contained the αA-crystallin promoter fused to the T-antigen gene of SV40. The lenses of these mice were neoplastically transformed, showing for the first time that the lens is not refractive to cancer, as was long believed. More importantly, the transgenic mice experiments established that crystallin promoters can be used to modify lens genotype and phenotype by genetic engineering. In addition, our results suggest strongly that regulatory sequences for other genes, for example S-antigen or opsin which are expressed in the retina, can also be used to direct foreign genes to different ocular tissues. Thus, it has become possible to consider genetic engineering for both basic and potentially clinical investigations on the eye. We are in the process of developing a facility to produce transgenic mice in our laboratory. Dr. Ana Chepelinsky has been very much involved in this effort. Hopefully, FY 1987 will witness the birth of many interesting LMDB transgenic mice.

Finally, the ARVO electorate has been kind to us this year. Dr. Peggy Zelenka has been elected to the program committee (1987-1989) of the Lens Section and I have been elected as a trustee (1986-1990) representing the Lens Section. This will give the LMDB an administrative voice contributing to the advancement of vision research. Numerous collaborations with other laboratories (listed in the individual reports) have expanded our scope of research and are much appreciated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00127-10 LMDB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Plasma Membrane Composition and Biosynthesis in Chick Lens Fibers and Epithelia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Peggy Zelenka	Ph.D.	Geneticist	LMDB, NEI
	Luke Pallansch	Ph.D.	Staff Fellow	LMDB, NEI
	Malini Vatal	Ph.D.	Visiting Fellow	LMDB, NEI
	Jodell Boyle	B.S.	Medical Student	HHMI

COOPERATING UNITS *(if any)*

Beltsville Agricultural Research Center, Betlsville, MD (A. Ferretti)

LAB/BRANCH

Laboratory of Molecular and Development Biology

SECTION

Section on Cellular Differentiation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.3	1.5	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project seeks to determine whether the regulation of lens fiber differentiation and maturation is associated with alterations in the plasma membrane. The composition, biosynthesis, and metabolism of lens lipids have been investigated using embryonic and adult chicken lenses, and cultured lens epithelial cells derived from the Nakano mouse. The rate of degradation of the membrane phospholipid, phosphatidylinositol, has been shown to be tightly coupled to the rate of lens epithelial cell division and to cease when the epithelial cells differentiate to form lens fibers. Cultured lens epithelial cells and cultured fibroblasts have been shown to possess a mechanism for the rapid, transient gradation of phosphatidylinositol, which is independent of phospholipase C or phospholipase A_2. A similar pathway may play a role in the differentiation of lens epithelial cells into lens fibers. Since phosphatidylinositol is rich in arachidonic acid, a precursor of prostaglandins and leukotrienes, the metabolities of arachidonic acid produced by lens epithelial cells are being characterized in an effort to understand the physiological role of phosphatidylinositol degradation. Analysis of the archadonic acid metabolities of cultured lens epithelial cells of several species revealed the presence of both cyclo-oxygenase and lipoxygenase products, including prostagladins E_2 and $F_{2\alpha}$, and leukotrienes. All lens epithelial cell types examined synthesized products of the 5-lipoxygenase pathway of arachidonic acid metabolism. One product of this pathway, 5-hydroxytetraenoic acid, was weakly mitogenic when added to cultured lens epithelial cells in the absence of serum or growth factors. Alterations in phosphatidylinositol metabolism and in the production of arachidonic acid metabolities are being correlated with the action of growth factors in regulating cell division and differentiation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00238-01 LMDB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Proto-oncogene Expression During Lens Differentiation and Development

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Peggy Zelenka	Ph.D.	Geneticist	LMDB, NEI
Others:	Luke Pallansch	Ph.D.	Staff Fellow	LMDB, NEI
	Malini Vatal	Ph.D.	Visiting Fellow	LMDB, NEI
	Pravendra Nath	Ph.D.	Visiting Fellow	LMDB, NEI

COOPERATING UNITS *(if any)*

David C. Beebe	Ph.D.	Uniformed Services University of the Health Sciences Bethesda, MD

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Cellular Differentiation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.0	1.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project investigates the expression of proto-oncogenes during the differentiation of embryonic lens epithelial cells to form lens fiber cells, and seeks to determine the specific function of the corresponding gene products in the developing lens. Using radioactivity labeled DNA probes we have shown that mRNA levels for two proto-oncogenes, c-myc and c-src, are specifically regulated during the differentiation of chicken embryo lens epithelial cells to form lens fiber cells, both in vivo and in vitro. Levels of c-myc mRNA are transiently elevated during the first few hours after the initiation of differentiation in vitro, as the differentiating cells withdraw from the cell cycle. Since the c-myc gene product is a nuclear, DNA-binding protein, the transient elevation of c-myc mRNA in differentiating lens cells may lead to the regulation of other, differentiation-specific genes. Levels of c-src mRNA rise more slowly than levels of c-myc mRNA, and remain elevated in the mon-dividing embryonic fiber cells. The c-src gene product is a tyrosine-specific protein kinase, the substrates of which we are presently investigating in the developing embryonic chicken lens.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00132-05 LMDB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Biology of Photopigments

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Toshimichi Shinohara	Ph.D.	Head	LMDB, NEI
Others:	Graeme Wistow	Ph.D.	Visiting Fellow	LMDB, NEI
	Albine Katial	Ph.D.	Staff Fellow	LMDB, NEI
	Cheryl Craft	Ph.D.	Guest Worker	LDN, NICHD
	Masahiko Tsuda	M.D., Ph.D.	Visiting Fellow	LMDB, NEI
	Theo Van Veen	Ph.D.	Guest Worker	LRCMB, NEI

COOPERATING UNITS *(if any)*

See next page

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Molecular Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.4	3.4	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have examined the structure, function, development evolution, epitopes and uveitogenic site of the retinal S-antigen (48k protein). The cDNAs of S-antigen have been isolated from bovine retina libraries and their DNA sequences have been determined. The predicted amino acid sequence was matched completely with that of S-antigen determined by Edman degradation method. S-antigen polypeptide has some sequence homologies with Gα-transducin including the cholera toxin, pertussis toxin and enterotoxin ADP-ribosylation sites and purine nucleotide-binding sites. S-antigen is found to be a glycoprotein and its sugar moeity is glucose and mannose. Secondary structure prediction and circular dichroism analysis indicated that S-antigen has a predominantly extended (β-sheet) structure with a small C-terminal helical region. The location of the two monoclonal antibodies binding sites and the one uveitogenic site of S-antigen has been determined. These three linear immunogenic sites were localized within 20 amino acid residues at three separated sites. The mRNA of S-antigen is approximately 2 kb long and present in the rod cells but not present in the majority of cone cells. The majority of mRNA was found very close to the nucleus but not found in the most part of myoid and ellipoid of the rod inner segments. Also S-antigen mRNA was present in certain types of pinealocytes. S-antigen has only one gene in mouse and human, indicating that the S-antigen of retina and pineal is the same. The S-antigen genes of human and mouse were isolated and identified by partial DNA sequences and the human S-antigen gene is located on the chromosome No. 14.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00126-05 LMDB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Crystallin Genes: Structure, Organization, Expression, and Evolution

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Joram Piatigorsky	Ph.D.	Chief	LMDB, NEI
	Ana B. Chepelinsky	Ph.D.	Expert	LMDB, NEI
	Graeme J. Wistow	Ph.D.	Visiting Associate	LMDB, NEI
	John F. Klement	Ph.D.	Staff Fellow	LMDB, NEI
	Mark A. Thompson	Ph.D.	Staff Fellow	LMDB, NEI
	Charlotte A. Peterson	Ph.D.	Guest Worker	LMDB, NEI
	Eric F. Wawrousek	Ph.D.	Staff Fellow	LMDB, NEI

COOPERATING UNITS *(if any)*

See next page.

LAB/BRANCH
Laboratory of Molecular and Developmental Biolgy

SECTION
Section on Molecular Genetics

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
13.0	13.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have continued to characterize the structure, expression and evolution of crystallin genes of the eye lens. Sequences have been obtained for the βB1-, βA3/A1- and β2-crystallin chicken cDNAs. Gene sequences have been derived for chicken and human αA-crystallin chicken βB1- and βA3/A1-crystallin, and chicken δ-crystallin. Both chicken δ-crystallin polypeptides were shown to be generated from the δ1 mRNA by a translational or co-translational mechanism. Transfection experiments demonstrated that the alternative RNA splicing of the murine αA-crystallin gene is neither tissue- nor species-specific. Crystallin promoters were analyzed by fusion to the bacterial chloramphenicol acetyl transferase (CAT) gene in the pSVO-CAT expression vector. Cell-free transcription experiments using a Hela cell extract was used to identify the core promoter of the chicken δ- and murine αA-crystallin promoters. Transient transfection experiments using cultured lens epithelia and production of transgenic mice demonstrated tissue-specific and developmental controls operating in the crystallin promoters. Both positive and putative negative regulatory sequences were indicated. The murine αA-crystallin promoter (sequences -364 to +45) when fused to the SV40 T-antigen gene neoplastically transformed lens cells in transgenic mice. Thus, these experiments initiate genetic engineering in the visual system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00078-09 LOP

PERIOD COVERED

October 1, 1985, to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Histopathology of Human Dystrophies and Degeneration

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Merlyn M. Rodrigues	M.D.,Ph.D.	Head, Section on Ophthalmic Pathology	LOP, NEI
Others:	Joseph Hackett	B.S.	Biologist	LOP, NEI
	Reginald Gaskins		Histologist	LOP, NEI

COOPERATING UNITS *(if any)*

Department of Ophthalmology, University of Iowa, Iowa City

LAB/BRANCH

Laboratory of Ophthalmic Pathology

SECTION

Section on Ophthalmic Pathology

INSTITUTE AND LOCATION

National Eye Institute, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human corneal dystrophies and degenerations which have been clinically documented are studied as keratoplasty specimens with histochemical stains, scanning and transmission electron microscopy, and immunologic techniques in an attempt to elucidate pathogenetic mechanisms. This approach has provided insight into cell-to-cell relationships in the normal and diseased states. In patients with primary and recurrent macular corneal dystrophy, intercellular and extracellular accumulation of fibrillogranular material was observed in the corneal stroma, Descemet's membrane, and corneal endothelium. The presence and production of collagen, glycoconjugates, and collagenase have been investigated with immunofluorescent electrophoretic, and chromatographic methods. The lectin binding patterns were compared in corneas from patients with macular dystrophy and control. The characterization of amyloid in lattice corneal dystrophy and corneal amyloid degeneration was performed using immunohistochemical stains and biochemical analysis. Lack of AA reactivity was observed in corneal amyloid deposits. Keratoplasty specimens from granular corneal dystrophy and controls were examined by combinations of immunohistological stains, transmission electron microscopy, and SDS gel electrophoresis. In granular dystrophy, the deposits consisted of phospholipid with microfibrillar protein at the edges. Corneal buttons from patients with Fuchs' dystrophy had varying degrees of clinical edema measured in most cases by preoperative optical ultrasonic pachymetry. Histologically, marked thickening of Descemet's membrane and abnormal corneal endothelium corresponded to areas of severe clinical edema and were usually located in the central and paracentral regions. Clinical edema was not present unless accompanied by marked thickening of Descemet's membrane with multiple guttata and attenuation of corneal endothelium. The peripheral cornea was relatively clear clinically and showed minimal histologic changes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00096-08 LOP

PERIOD COVERED

October 1, 1985, to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinicopathologic Studies of Human Ocular Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Merlyn M. Rodrigues	M.D., Ph.D.	Head, Section on Ophthalmic Pathology	LOP, NEI
Others:	David Bardenstein	M.D.	Guest worker	LOP, NEI
	Joseph Hackett	B.S.	Biologist	LOP, NEI
	Reginald Gaskins		Histologist	LOP, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Ophthalmic Pathology

SECTION

Section on Ophthalmic Pathology

INSTITUTE AND LOCATION

National Eye Institute, NEI, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with localized ocular diseases or with ocular manifestations of systemic disease are examined clinically, and photographic documentation is made of significant findings. Biopsy specimens or autopsy eyes from these patients are examined by electron microscopy and histochemical stains. Studies are performed on patients with ocular manifestations of systemic diseases.

Forty patients with acquired immunodeficiency syndrome (AIDS) were examined for ocular abnormalities. Twenty of these patients died and the eyes were obtained for culture and histologic examination. These patients have multiple opportunistic infections and neoplasms as the result of a severe depression of cellular immunity. Fifty percent of all patients with AIDS and 75% of the autopsy group have ocular signs attributable to AIDS. Ocular findings were confined to four major categories: cytomegalovirus (CMV) retinitis (10 patients), retinal cotton wool spots (11 patients), conjunctival Kaposi's sarcoma (2 patients), and neuro-ophthalmic motility abnormalities (3 patients). Cytomegalovirus retinitis was a significant cause of visual loss. Seven of 40 autopsy eyes had hand-motion or worse vision prior to the patient's death because of CMV and progressed to involve the entire retina in three to six months resulting in a gliotic retina membrane. Disseminated systemic histoplasmosis was observed in a patient with AIDS. In 3 patients, the effect of argon laser treatment was shown to be ineffective in halting the spread of cytomegalovirus in patients with AIDS.

Immunohistochemical stains are performed on patients with retinitis pigmentosa and retinoblastoma to test for the presence of neuronal and glial proteins. Electron microscopy is also performed in selected cases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00114-06 LOP

PERIOD COVERED

October 1, 1985, to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Histopathologic Studies of Animal Models of Human Ocular Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)*

PI:	Merlyn M. Rodrigues	M.D.,Ph.D.	Head, Section on Ophthalmic Pathology	LOP, NEI
Others:	Reginald Gaskins		Histologist	LOP, NEI
	Joseph Hackett	B.S	Biologist	LOP, NEI
	Anastasios Halkias	M.D.	Fogarty Fellow	LOP, NEI
	Barbara Wiggert	Ph.D.	Research Chemist	LVR, NEI
	Gerald Chader	Ph.D.	Chief, Laboratory of Vision Research	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Ophthalmic Pathology

SECTION

Section on Ophthalmic Pathology

INSTITUTE AND LOCATION

National Eye Institute, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Immunocytochemical staining of fresh frozen rhesus monkey retinas was performed using indirect immunofluorescence and immunoperoxidase (avidin-biotin-complex). Affinity-purified antibodies to interphotoreceptor retinoid-binding protein (IRBP) obtained from rabbits was used to localize IRBP on frozen sections. Fresh frozen pineal glands from the same species were stained by the avidin-biotin-peroxidase method. In addition, retinas from rod-dominant and cone-dominant species were examined. Immunocytochemical staining revealed localization of IRBP in the interphotoreceptor space of peripheral equatorial and posterior retina, with marked decrease in staining in the fovea. A transition zone was noted at the ora serrata, where staining was present in the peripheral retina up to the ora serrata, but was absent in ciliary epithelium. Cone-dominant retinas (chick and turtle) showed lack of reactivity to IRBP. Rod-dominant rat retina showed localization of IRBP to the interphotoreceptor space. Primate and rat pineal showed immunocytochemical localization of IRBP. Spontaneously occurring anterior chamber segment anomalies in DBA/2 mice were studied by slit-lamp biomicroscopy and light and transmission electron microscopy (TEM). The opacities consisted of aggregates of basophilic material in the superficial stroma which stained positively for elastin TEM revealed that they were electron dense and extracellular. Iris abnormalities consisted of stromal atrophy and proliferation of corneal endothelium and basement membrane across the iris surface and trabecular meshwork. The corneal opacities seen in DBA/2 mice show a striking similarity to those which characterize familial band-shaped nodular keratopathy, a form of corneal elastosis.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1985 - September 30, 1986

REPORT OF THE CHIEF, LABORATORY OF RETINAL CELL AND MOLECULAR BIOLOGY

Gerald J. Chader, Ph.D.

The Laboratory of Retinal Cell and Molecular Biology is a newly formed unit within the National Eye Institute. It draws together former members of the Laboratory of Vision Research who have a common interest in basic and applied studies on the neural retina and associated tissues such as pigment epithelium. As the name implies, aspects of retinal cell biology as well as molecular biology are being studied both in normal and in diseased tissues. In particular, there is an emphasis on the study of inherited retinal diseases as exemplified by retinitis pigmentosa and retinoblastoma.

The laboratory consists of three separate but cooperating Sections each investigating a particular aspect of retinal function. Following are highlights of some of the research conducted by members of the LRCMB over the last year:

Section on Cell Biology: As Chief of this section, Dr. Paul O'Brien leads the NEI effort in studying unique biochemical events in the retina related to photoreceptor physiology. In normal retinas, he has continued to define specific reactions leading to acylation of rhodopsin, the visual pigment. Palmitate is added to newly synthesized as well as mature rhodopsin molecules and may be involved in important cellular processes such as sorting and transport of protein from the Golgi apparatus and in disc membrane assembly and outer segment membrane repair mechanisms. In parallel, he has been investigating synthesis and degradation of proteins and phospholipids in normal retinas and in animal models of inherited retinal degeneration. Of potential importance is the apparently abnormal phospholipid metabolism that Dr. O'Brien has now observed in poodles affected with inherited rod-cone degeneration. These animals exhibit an abnormally low rate of photoreceptor outer segment renewal prior to the onset of degeneration.

Section on Biochemistry: Dr. Barbara Wiggert has continued her impressive work on the biochemistry and function of IRBP, the interphotoreceptor retinoid-binding protein. It is now clear that this protein is a unique, new type of retinoid transport protein designed for the extracellular transport of retinoids between the photoreceptor elements of the neural retina and vitamin A stores in the retinal pigment epithelium. This work takes on added significance with the discovery of substantial amounts of IRBP in the pineal organs of several species. Although the function of the protein in the pineal gland in presently not clear, it may indicate a hitherto unknown role of retinoids and their transport in this secondary organ of phototransduction.

Section on Gene Regulation: In collaboration with Dr. Wiggert, Dr. John Nickerson and his group have made excellent progress in studying the molecular biology of the IRBP molecule. cDNAs for IRBP, for example, have now been established and verified and about one half of the nucleotide sequence has been determined. Bovine and human genomic clones have also been established and progress has been made concerning the chromosomal location of the IRBP gene. Aspects of IRBP synthesis are also under investigation. It is of interest that the size of the IRBP mRNA is extraordinarily large, indicating a long uncoded region. In situ hybridization studies have indicated that the probable site of IRBP synthesis in the retina is predominantly in the rod photoreceptor cell. These studies further strengthen the argument that IRBP is intimately involved in general processes of photoreception.

Other members of the Section on Gene Regulation have focused their work on attempting to find the biochemical lesion(s) in animals exhibiting early-onset retinal degeneration. In particular, Mr. R.T. Fletcher has studied genetic crosses of rd and rds mice with reference to the cyclic GMP second messenger system in photoreceptor cells and has found a direct gene-dose relationship between a photoreceptor cell cyclic GMP phosphodiesterase enzyme and the rds gene. This would seem to be of importance in linking abnormal retinal concentrations of cyclic GMP with the rds gene responsible for degeneration of the retina.

Another hereditary disease under investigation is retinoblastoma. Dr. A. Kyritsis has made substantial progress in understanding factors related to growth and differentiation of human Y-79 retinoblastoma cells in culture. One of the most controversial questions concerning this type of cancer over the years, has been the origin of the cells. From Dr. Kyritsis' work, it now appears that the cells are multipotential blast cells capable of at least partial differentiation into most if not all of the general cell types found in the normal retina. These include neuronal, glial and pigment epithelial elements. This has been a particularly satisfying finding, since it explains most of the seemingly contradictory previous evidence in the literature and it indicates that the tumor cells, depending on their particular surroundings (substratum, differentiating agents, etc.), can develop along any one or more of these pathways as the tumor grows.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00070-09 LRCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Vitamin A and Ocular Tissues

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Barbara Wiggert	Ph.D.	Head, Section on Biochemistry	LRCMB, NEI
Others:	Ling Lee	M.S.	Chemist	LRCMB, NEI
	Michael Redmond	Ph.D.	Staff Fellow	LRCMB, NEI
	Gerald J. Chader	Ph.D.	Chief	LRCMB, NEI

COOPERATING UNITS *(if any)*

LSU Eye Center, New Orleans, LA (N. Bazan, T. Reddy)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Biochemistry

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.7	1.7	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An enzyme-linked immunosorbent assay (ELISA) for monkey and human Interphotoreceptor Retinoid-Binding Protein (IRBP) was used to quantitate IRBP in normal and diseased human retinas and retinoblastoma tumors. IRBP levels were uniformly low in retinas from human cases of hereditary retinal degenerations even in areas in which photoreceptors remained. IRBP was present in several retinoblastoma tumors examined.

The amino terminal sequences of monkey and bovine IRBPs were extended to over 30 residues each. The major monkey sequence had an additional 5 amino acid residues at its amino terminus not observed with bovine IRBP, although the sequences showed extensive homology. The amino terminal sequence of human IRBP was identical to that of the monkey, and the two sequences were present in equal amount.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00015-21 LRCMB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Cell Biology of the Vertebrate Retina

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Paul J. O'Brien	Ph.D.	Head, Section on Cell Biology	LRCMB, NEI
Others:	Robert St. Jules	Ph.D.	Staff Fellow	LRCMB, NEI

COOPERATING UNITS *(if any)*

Department of Anatomy, University of Toronto (M. J. Irons)

LAB/BRANCH
Laboratory of Retinal Cell and Molecular Biology

SECTION
Section on Cell Biology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.6	1.6	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The acylation of rhodopsin with palmitic acid has been studied to determine the function of this modification in the intracellular transport of rhodopsin and its incorporation into functional disc membranes. Palmitate is added to rhodopsin shortly after the polypeptide is synthesized. Most of the new rhodopsin molecules are retained in the endoplasmic reticulum for at least six hours, suggesting that transport to the outer segment may not be a continuous process. Palmitate is also added to mature rhodopsin molecules in the outer segment indicating a possible repair mechanism or a physiologically important cycle of removal and replacement. The phospholipids of the outer segment turn over continuously but retain and, in the case of phosphatidylethanolamine, even increase the level of labeling with palmitic acid. Thus, this fatty acid undergoes a continuous process of reutilization.

Cytidine monophosphate, a by-product of phospholipid turnover, is cleaved by a manganese-dependent nucleotidase in rod outer segments. Histochemical studies indicate that this enzyme is transported from the pigment epithelium to the outer segments in anticipation of disc shedding and may represent a class of degradative enzymes involved in this process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00016-19 LRCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Biochemistry of Normal and Dystrophic Retinas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Paul J. O'Brien	Ph.D.	Head, Section on Cell Biology	LRCMB, NEI
Others:	Peter A. Dudley	Ph.D.		ECP, NEI

COOPERATING UNITS *(if any)*

School of Veterinary Medicine, University of Pennsylvania (G. Aguirre)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Cell Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.2	0.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project examines biochemical events unique to the retina, particularly the synthesis and modification of photoreceptor membrane components, in the retinas of vertebrates which can be affected by inherited retinal degenerations. The synthesis of the visual pigment, rhodopsin, occurs at a normal rate as measured by radioactive leucine incorporation following intravitreal injection in the eyes of miniature poodles affected with progressive rod-cone degeneration. Similarly, the glycosylation and acylation of rhodopsin were found to be normal following intravitreal injection of labeled fucose or palmitic acid, respectively. However, phospholipid synthesis or degradation, measured by radioactive palmitic acid incorporation, appears to be different in the affected dogs, suggesting a possible metabolic defect in this inherited disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00148-13 LRCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cyclic Nucleotides and Visual Control Mechanisms

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Gerald J. Chader	Ph.D.	Chief	LRCMB, NEI
Others:	Susan Gentleman	Ph.D.	Expert	LRCMB, NEI
	R. Theodore Fletcher	M.S.	Chemist	LRCMB, NEI
	Robert L. Somers	B.S.	Chemist	LRCMB, NEI
	C. Lal Kapoor	Ph.D.	Guest Worker	LRCMB, NEI

COOPERATING UNITS *(if any)*

Section on Medical Genetics, School of Veterinary Medicine, University of Pennsylvania (G. Aguirre); Department of Anatomy, Erasmus University, Rotterdam, The Netherlands (S. Sanyal)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Gene Regulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.8	1.8	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cyclic nucleotides and protein phosphorylation play a special role in photoreceptor control mechanisms.

1. A calcium phospholipid-dependent protein kinase (C-kinase) phosphorylates specific proteins of the rod outer segment organelle.
2. A specific extracellular cyclic GMP phosphodiesterase was identified in the retinal extracellular matrix.
3. Cyclic AMP-dependent protein kinases were found to be abnormal in human retinoblastoma cells in culture.
4. Cyclic GMP was found to be abnormally high in photoreceptor cell synapses of an animal model of inherited retinal degeneration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00124-06 LRCMB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Metabolism of the Retina and Pigment Epithelium

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Gerald J. Chader	Ph.D.	Chief	LRCMB, NEI
Others:	Shay-Whey M. Koh	Ph.D.	Staff Fellow	LRCMB, NEI
	Athanassios P. Kyritsis	M.D.	Visiting Fellow	LRCMB, NEI
	R. Theodore Fletcher	M.S.	Chemist	LRCMB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Retinal Cell and Molecular Biology

SECTION
Section on Gene Regulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.1	2.1	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Metabolic characteristics of retinal cells in tissue culture are under examination.

1. The response of cultured cells of the retinal pigment epithelium to various neurotransmitters and neuromodulators have been examined, especially to vasoactive intestinal peptide (VIP). A specific VIP receptor has been identified on pigment epithelial cell membranes; also, soluble and membrane proteins phosphorylated in response to VIP have been identified.
2. Human retinoblastoma cells in culture can be induced to differentiate in culture into the three major cell types seen in the normal retina, ie, neurons, glia and pigment epithelial cells. Laminin and appropriate other attachment factors appear to play a role in retinoblastoma cell differentiation as well as attachment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00196-03 LRCMB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Genetics of the Eye and Ocular Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John M. Nickerson	Ph.D.	Senior Staff Fellow	LRCMB, NEI
Others:	Diane Borst	Ph.D.	Guest Worker	LRCMB, NEI
	Shirley Rainier	Ph.D.	Staff Fellow	LRCMB, NEI
	T. Michael Redmond	Ph.D.	Staff Fellow	LRCMB, NEI

COOPERATING UNITS *(if any)*
Zoology Department, University of Lund, Lund, Sweden (Theo Van Veen)

LAB/BRANCH
Laboratory of Retinal Cell and Molecular Biology

SECTION
Section on Gene Regulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.5	2.5	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

My laboratory is presently isolating and characterizing recombinant DNA molecules necessary for the study of the structure and expression of IRBP (Interphotoreceptor Retinoid-Binding Protein). Clones and partial sequences from bovine IRBP have been obtained. We have cloned and completely sequenced six overlapping cDNA clones that constitute about 3500 bases of the 7000 base long bovine IRBP mRNA. The IRBP mRNA is unusually long especially given that the polypeptide encoding region of the mRNA should only require about 3600 bases. There is only one band on a Northern blot suggesting that there is only one IRBP mRNA species. The clones were used as probes for in situ hybridizations to frozen sections of bovine and monkey retinas. In large, only the rod cell perikarya were labelled with the probe. This showed us that the gene is regulated and expressed only in the rod cell, and it defined the site of synthesis of the IRBP polypeptide as the rod cell. Part of the gene for bovine IRBP has been cloned. Partial DNA sequence analysis revealed a perfect match of 75 bases of the cDNA and genomic clones. The sequences diverged at a consensus splice acceptor site in the gene clone, indicating an intron-exon boundary. We have obtained a putative genomic clone for the human gene, but it remains to be proven (by DNA sequencing) that this clone is authentic. We have begun to characterize the IRBP gene by analysis of Southern genomic blots. We have shown that the gene is present in only one copy per haploid genome in a variety of species. In human, the gene is not on the X-chromosome, since hybridizing bands from male and female DNA samples are the same intensity. We are now in the process of mapping the precise chromosome.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1985 - September 30, 1986

REPORT OF THE CHIEF, LABORATORY OF SENSORIMOTOR RESEARCH

Robert H. Wurtz, Ph.D.

This is the eighth Annual Report of the Laboratory of Sensorimotor Research and is intended to describe work in the Laboratory over the last two years. I would like in this somewhat more flexible report to concentrate on the relevance of work in the Laboratory to several fundamental problems of visual neuroscience. In particular, I would like to emphasize the contribution of our analysis of the visual and the oculomotor system in the monkey to an understanding of these systems in man.

The aspect of brain function that we study, the visual and oculomotor system, has been shown repeatedly to be very similar in man and monkey so that the experiments we perform on the monkey serve as a model for man. Behavioral, physiological, and anatomical experiments possible on the monkey have given us our most fundamental understanding of how the visual and oculomotor functions of the brain of man are likely to be organized. In addition I think several investigations in the Laboratory in the last several years illustrate how the precise analysis possible in the visual-oculomotor system has allowed exploration of fundamental questions in brain research.

One of these questions is how we are able to obtain sensory information in spite of the continual movements we make in our environment. The pinnacle of this stability is the ease with which we maintain stable vision in spite of our own movement of body, head, and eyes. Much of this stability of the eye is due to the vestibular-ocular reflex, a system that Dr. F. A. Miles in the Laboratory has studied over a period of years. In this system, the balance mechanisms in the ear lead to eye movement that compensates for head and body movement. In addition to this vestibular mechanism, another system has been studied by Dr. Miles that provides fine tuning of this stabilization. This ocular following response occurs with the incredibly short latency of only about 50 msec following a rapid or saccadic eye movement across a visually patterned environment. Furthermore, the ocular following is enhanced following such eye movements just at the time when increased stabilization of vision is essential. The mechanisms underlying this visual motor event can be dissected apart by replacing the rapid eye movement with an equally rapid shift in the visual environment: the ocular following response can still be invoked easily. However, when a large visual scene is quickly moved in a saccade-like way the ocular following response is actually suppressed. This powerful inhibitory mechanism that emanates from the peripheral visual field probably prevents the eye from tracking the visual disturbances created by the rapid eye movements as they sweep the visual scene across the retina. Thus, not one visual mechanism is involved in stabilization, but rather two interacting ones: one to produce the stabilization of the eye, the other to produce a suppression of that stabilization when it is inappropriate. These experiments demonstrate graphically the series of exact and elaborate mechanisms that primates use to maintain the essential conditions for normal vision. The

deficits in this type of stabilization, which may occur with the diseases of man, can only begin to be diagnosed if the series of interlocking mechanisms is clearly understood and this understanding can only be derived from the type of carefully controlled experiments such as those of Dr. Miles.

Effective vision not only demands stability during periods of fixation on a given object, but it also demands the ability to shift the highly developed central or foveal region of the retina from one part of the visual field to another. This selective function, frequently referred to as selective visual attention, has been studied over a number of years in the Laboratory. Dr. D. L. Robinson and his collaborators have continued this work in both monkey and man. His previous physiological experiments had shown that a region of cerebral cortex, the posterior parietal cortex, was critically involved in tasks related to attention, and that the pulvinar nuclei of the thalamus, a step on the visual pathway reaching from the brainstem to parietal cortex, were also critically involved in this selective attention mechanism. This behavioral attention in monkeys can be studied by giving the monkey a cue indicating the area of the visual field that is important and then testing the speed of a monkey's subsequent response to a stimulus in that field. By suppressing the activity of one area area of the brain with minute injections of chemicals while the monkey performs this task, Dr. Robinson has been able to show the involvement of that area of the brain in this type of selective attention. These methods of behavior testing have now been extended to human patients whose disease might involve the areas of the brain identified in the monkey as being related to visual attention. The tests have provided a constellation of deficits that characterize patients with lesions of the parietal area of cerebral cortex. In contrast, patients suffering from schizophrenia or from Alzheimer's disease might show some deficits in attentional tasks, but not the same set of deficits seen in those patients with parietal lesions. Thus, a set of experiments growing out of an analysis of the neural systems within the brain of monkeys has been developed that allows the diagnosis of damage to one part of the brain of man. Furthermore, this analysis of visual attention shows that the highest level of behavior in man can be subjected to precise behavioral analysis and related to precise neural structures within the brain.

Possibly the region of the cerebral cortex involved in the highest neural processing is the frontal lobe, and it is in this region that Dr. M. E. Goldberg and his collaborators have concentrated their analysis of one type of eye movement, the rapid, or saccadic eye movements which I have referred to above. The pathways for this particular type of movement, that connects the visual signals arriving from the eye to the activation of the eye muscle to move the eye towards the target, is probably the best understood sensorimotor pathway within the brain. What is striking about this system is that there seems to be a separate segment related to the same movement made under different conditions: some areas of the brain participate in the generation of all saccades; others participate only in saccades that are important to an animal's behavior, whether or not the saccades are made in response to visual targets. The frontal cortex seems to be particularly important for this latter type of movement. The frontal eye fields do not, however, send a motor message for the generation of saccades irrelevant to a subject's behavior. Ordinarily, the act of attentive fixation filters out the signals for irrelevant saccades. Thus Dr. Goldberg and his group found that it was more difficult to evoke saccades electrically from the frontal eye fields when a monkey was actively looking at a spot of light, and the saccade evoked had a characteristic waveform called a square-wave jerk. In collaboration with the

Neuro-Ophthalmology Section, Dr. Goldberg noticed that certain patients complaining of slow reading made square-wave jerks while they attempted to fixate a target. Since these eye movements resemble those evoked in the monkey during attentive fixation, they might in man be a sign of attentional fluctuations, which would make the oculomotor system more susceptible to signals for irrelevant saccades. Since other patients with cerebellar disease have square-wave jerks but no reading difficulty, Dr. Goldberg hypothesized that the deficit was not oculomotor instability but rather an attentional deficit which interfered both with adequate oculomotor performance and reading. A small number of these patients were treated with methylphenidate, a drug approved for attentional deficit disorders. Not only did the square-wave jerks disappear, but several measures of reading performance also improved under treatment. This promising new line of clinical research in man would not have been possible without the fundamental observations on the frontal eye fields of monkeys.

Visual processing in both man and monkey is represented in other regions of the cerebral cortex, primarily in the occipital and temporal lobes. One of the most promising developments in our understanding of this visual processing has been the realization that the analysis might be divided between different subregions of this region of cerebral cortex. My collaborators and I have studied one aspect of this visual processing, that related to visual motion processing and its relationship to a type of eye movement that is dependent on such motion, the generation of smooth pursuit eye movements. These movements are used to follow a slowly moving target in order to keep the target positioned upon the fovea. It is interesting to note that this type of eye movement evolves most clearly in primates so that in order to study the system in man, one must analyze the mechanisms in another primate such as the monkey. Our experiments have demonstrated that minute chemical removal of cells in the motion area of cerebral cortex reduces a monkey's ability to generate pursuit eye movements. Furthermore, similar damage to the next step of visual processing produces an additional deficit, a difficulty in keeping the eye on the target once it is on the fovea but only when the target moves toward the damaged side of the brain. It is striking that one of the first deficits related to eye movements in man that was specifically related to the cerebral cortex was this directed pursuit deficit. Thus, with minute lesions in monkeys, we have been able to replicate the deficits seen following the uncontrolled and extensive accidents of nature in man. Furthermore, because we are able to analyze the response of single cells in the monkey, we have been able to see the types of cells in a sequence of visual areas, including those areas producing the directional deficit. The hypothesis that we have developed suggests that the first visual area is related to visual motion processing while the next one (related to the directional deficit) has signals related to maintaining eye movements that do not depend on the visual input. These experiments demonstrate the use of a particular type of eye movement in the analysis of visual processing; the removal of a tiny visual area leads to an exactly measurable deficit in the eye movement. Tight coupling between the visual and oculomotor system makes such an analysis possible in the visual system, and holds promise of precise localization of visual function even within the cerebral cortex.

Finally, in the studies considered so far, the response of neurons has generally been taken as the total number of electrical discharges produced in response to a given visual stimulus, or in relation to a particular eye movement. However, the work of Dr. L. M. Optican in this Laboratory and Dr. B. J. Richmond in the Institute of Mental Health have called this assumption into question at

least as far as the visual analysis related to form perception is concerned. They have analyzed the distribution of electrical discharges of cerebral cortex cells following the presentation of a systematically varied visual stimulus. They find that while the rate of discharge conveys information about the visual stimulation, the amount of information conveyed by the pattern of discharges is twice that carried if one looks at the number of discharges alone. They show that in a given cell several independent patterns of spike activity are produced by the set of stimuli they used and that these patterns exist simultaneously. These experiments in turn led Optican and Richmond to formulate a new hypothesis about how information is transmitted in the visual system. They propose that these neurons each act as simultaneously active but independent spatial to temporal filters. Each filter generates a component of the visual response, and these components are then combined to form the spike train. While the underlying principle of multiple, simultaneous filtering operations has been demonstrated for neurons in the primary striate cortex and the inferior temporal cortex, the same mechanism may be functioning in other systems as well. Thus, in the case of the visual system, where the stimulation can be very exactly controlled using a mathematically definable set of stimuli, it has been possible to relate the temporal pattern of cell discharge to the sensory stimulation. The extent and importance of this type of information transmission in the visual system remains almost totally unexplored, but represents an exciting possible neuromechanism that may help us to understand the way in which the complexities of vision are represented within the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00049-08 LSR

PERIOD COVERED

October 1, 1985, to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cerebral Cortical Mechanisms for Eye Movements and Visual Attention

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Michael E. Goldberg	M.D.	Chief, NMS	LSR, NEI
Others:	Mark Segraves	Ph.D.	Staff Fellow	LSR, NEI
	Deng Shu-yi	M.D., Ph.D.	Visiting Fellow	LSR, NEI
	Rolf Boch	Ph.D.	Visiting Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

Department of Anatomy, Howard University (G. B. Stanton)

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Neuro-Ophthalmologic Mechanisms Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.9	3.8	1.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

By antidromic stimulation in the superior colliculus of neurons in the arcuate frontal eye fields, it was determined that cells bearing eye movement or fixation signals but not those with peripheral visual information project to the superior colliculus from the frontal cortex. This implies that the cerebral cortex sends only a motor message to the brainstem saccadic eye movement system.

Monkeys trained on a saccadic adaptation paradigm learn quickly to change the amplitude of their saccades in response to intrasaccadic stimulus steps. Stimulation of the superior colliculus in the adapted case yields the same saccades as the unadapted case. The activity of single neurons also shows no evidence of adaptation: the visual and movement signals emanating from the colliculus are the veridical signals for stimulus and movement, rather than movement signals in a visual frame which are modified by the brainstem. Thus the change in saccade amplitude which occurs as a result of adaptation is compensated for at early sites in the neural chain from stimulus to response.

A small percentage of humans with reading disorders have fixational instability manifest by saccadic intrusions or square-wave jerks while they attempt to fixate a spot of light. A single dose of methylphenidate decreases or eliminates the saccadic intrusions and results in temporary improves in both the ocular mechanics of oral reading and the reading performance itself.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00153-04 LSR

PERIOD COVERED

October 1, 1985, to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Adaptive Regulation in Primate Oculomotor System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Frederick A. Miles	D.Phil	Chief, OCS	LSR, NEI
Others:	Lance Optican	Ph.D.	Senior Staff Fellow	LSR, NEI
	Reuben Gellman	Ph.D.	Visiting Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Oculomotor Control Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.5	1.5	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Experiments were concerned with the initial ocular following responses to transient ramp movements of the visual scene in monkeys. These tracking movements are important in the stabilization of gaze which is so necessary for good visual acuity. We had previously shown in monkeys that responses have short latency (50 msec) and are transiently enhanced after saccadic eye movements due to the associated visual disturbance. We now report that saccadic eye movements are also associated with powerful inhibitory effects on ocular following. This inhibition was shown to be visual in origin and to result from stimulation of the peripheral region of the visual field. For these experiments the visual field was partitioned into central and peripheral regions (center, 20° diameter). Sudden shifts of the peripheral images elicited brief, powerful inhibition of ocular following responses generated by test stimuli at the center. This peripheral suppression showed good intraocular transfer: saccade-like movements of the peripheral field of one eye suppressed the responses elicited by test ramps applied at the center of the other eye. These data indicate that the suppression involves lateral spatial interactions at/or beyond a site that receives input from the two eyes, and hence, must be mediated by the central nervous system. We suggest that this suppression functions to prevent the ocular following system from tracking the visual disturbances caused by saccades: saccade-like movements of the central field alone produced small transient ocular following responses whereas such movements of the periphery or of the whole field did not.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00152-04 LSR

PERIOD COVERED

October 1, 1985, to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Visually Induced Adaptive Changes in Saccadic Innervation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Lance Optican Ph.D. Res. Biomedical Engineer LSR, NEI

Others: Frederick A. Miles D.Phil. Chief, OCS LSR, NEI

COOPERATING UNITS *(if any)*

David S. Zee, M.D., Professor Neurology,
Johns Hopkins School of Medicine, Baltimore, MD

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Oculomotor Control Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.8	0.8	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Saccades are the rapid eye movements used to change visual fixation. These eye movements are very fast yet they end abruptly, i.e., the eyes do not drift at the end of a saccade. This lack of post-saccadic drift is essential for good visual acuity after a saccade. Previous experiments in this laboratory have shown that the brain actively suppresses post-saccadic drift by altering the levels of innervation sent to the muscles during and after a saccade. The adaptive mechanism for suppression of post-saccadic drift is sensitive to optically-imposed post-saccadic retinal slip. Our previous work showed that a central neural mechanism attempted to compensate for this post-saccadic retinal slip by altering the gain and time constants of the neural components of saccadic innervation. This altered innervation led to a post-saccadic ocular drift that lessened the amount of post-saccadic retinal slip.

We have previously shown that this central adaptive mechanism was dependent upon the cerebellum for its proper function. After a complete cerebellectomy, monkeys developed post-saccadic ocular drift, and were unable to compensate for post-saccadic retinal slip. The present work has now shown that the site of this functional dependency can be further localized to the cerebellar flocculi and paraflocculi.

After bilateral flocculectomy, monkeys developed post-saccadic ocular drift. When presented with optically-imposed post-saccadic retinal slip, the animals were only able to alter their saccadic innervations a little. These post-flocculectomy alterations were not large enough to compensate for the retinal slip. Furthermore, this ability was asymmetric, with reductions in gain being larger than increases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00045-08 LSR

PERIOD COVERED

October 1, 1985, to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Visuomotor Properties of Neurons in the Thalamus

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	David Lee Robinson	Ph.D.	Research Physiologist	LSR, NEI
Others:	John W. McClurkin	Ph.D.	Guest Worker	LSR, NEI
	Jon Currie	M.D.	Neuro-Ophthalmologist	LSR, NEI
	Mortimer Mishkin	Ph.D.	Laboratory Chief	LNP, NIMH
	Marcie Golomb	O.D.	Guest Worker	LSR, NEI
	Richard Sherins	M.D.	Res. Endocrinologist	RR, NICHD
	Edmond FitzGibbon	M.D.	Clinical Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Visuomotor Integration Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.6	1.0	1.6

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have studied visual spatial attention in humans and monkeys to determine what brain areas are important and what each contributes to this cognitive function. Visual cues which precede visual targets can modulate reaction times to the targets. Cues on the same side as the target (valid cues) are associated with fast reaction times; cues on the opposite side (invalid cues) or weak illumination of the entire visual field (diffuse cues) are correlated with slow reaction times. The cues are hypothesized to control the direction of the subject's attention.

Patients with damage to parietal cortex have slowed reaction times to targets which follow diffuse cues or to those cues which draw their attention to the intact visual field. These are both diffuse cues and one invalid cue. We have demonstrated the same deficit in the monkey after surgical removal of cortical area 7. This allows us to study directly a region of cortex in the monkey which is critical for visual spatial attention. Normal human controls or patients with temporal lobe damage do not have these problems. Humans with Alzheimer's dementia are extremely slow in all aspects of this task. Males with idiopathic hypogonadotropic hypogonadism have unusual patterns of responding on our attention task; they are slow in responding to all targets in their right visual field, independent of the preceding cue. They are also slow in responding to targets after diffuse cues.

These studies have helped to localize an area of the brain, the inferior parietal lobule, which is critical for visual spatial attention and helped to clarify its contribution to this cognitive process. In addition they have demonstrated a possible endocrine influence on visual behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00109-06 LSR

PERIOD COVERED

October 1, 1985, to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Visual Motion Processing in the Primate Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert H. Wurtz	Ph.D.	Chief	LSR, NEI
Others:	Max R. Dursteler	M.D.	Visiting Scientist	LSR, NEI
	Hidehiko Komatsu	Ph.D.	Visiting Scientist	LSR, NEI
	Dwayne S. Yamasaki	Ph.D.	Guest Researcher	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Visuomotor Integration Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.8	2.8	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Visual motion processing in the cerebral cortex of the monkey is carried out in a series of specialized areas. We have previously investigated one of these areas, the middle temporal area (MT) and we have now explored the next area, the medial superior temporal area (MST). We investigated the relation of motion processing to the generation of an eye movement that is dependent on such motion processing, smooth pursuit eye movements. We found cells that discharge during pursuit eye movements fell into two groups. Those that were dependent upon visual stimulation lie in the foveal region of MT and lateral MST, while those related to the movement itself were in the lateral and dorsal MST. Punctate removal of cells in these areas of MST using a neurotoxin, ibotenic acid, showed a deficit in pursuit initiation for targets moving in the contralateral visual field (a retinotopic deficit) and a deficit in maintenance of pursuit as long as the target was moving toward the side of the lesion (a directional deficit). We interpret the visual response of cells in MT and the retinotopic deficit as being related to visual stimulation (retinal slip) and the pursuit related cells and the directional deficit as being related to an efference copy signal of pursuit eye movements.